TOXICOLOGICAL PROFILE FOR
CYANIDE

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

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DISCLAIMER

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UPDATE STATEMENT

A Toxicological Profile for cyanide was released in April 1993. This edition supersedes any previously released draft or final profile.

Toxicological profiles are revised and republished as necessary, but no less than once every three years. For information regarding the update status of previously released profiles, contact ATSDR at:

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FOREWORD

This toxicological profile is prepared in accordance with guidelines* developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for the hazardous substance described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a hazardous substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staff of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

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*Legislative Background

The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed ATSDR to prepare toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. The availability of the revised priority list of 275 hazardous substances was announced in the *Federal Register* on April 29, 1996 (61 FR 18744). For prior versions of the list of substances, see *Federal Register* notices dated April 17, 1987 (52 FR 12866); October 20, 1988 (53 FR 41280); October 26, 1989 (54 FR 43619); October 17,1990 (55 FR 42067); October 17, 1991 (56 FR 52166); October 28, 1992 (57 FR 48801); and February 28, 1994 (59 FR 9486). Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1.   Green Border Review. Green Border review assures consistency with ATSDR policy.

2 .   Health Effects Review. The Health Effects Review Committee examines the health effects chapter
        of each profile for consistency and accuracy in interpreting health effects and classifying end
        points.

3.   Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to
        substance-specific minimal risk levels (MRLs), reviews the health effects database of each profile,
        and makes recommendations for derivation of MRLs.

PEER REVIEW

A peer review panel was assembled for cyanide. The panel consisted of the following members:

1.   Dr. Gary Isom, Professor of Toxicology, Department of Pharmacology and Toxicology, Purdue University, West Lafayette, Indiana;

2.   Dr. James Way, Professor of Pharmacology and Toxicology, Department of Medical Pharmacology and Toxicology, Texas A&M University, College Station, Texas; and

3.   Dr. Joseph Borowitz, Professor of Pathology, Department of Pharmacology and Toxicology, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, Indiana;

These experts collectively have knowledge of cyanide's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(i)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, *as* amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

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1. PUBLIC HEALTH STATEMENT

This public health statement tells you about cyanide and the effects of exposure.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites make up the National Priorities List (NPL) and are the sites targeted for long-term federal cleanup. Cyanide has been found in at least 84 of the 1,430 current or former NPL sites. However, it's unknown how many NPL sites have been evaluated for this substance. As more sites are evaluated, the sites with cyanide may increase. This information is important because exposure to this substance may harm you and because these sites may be sources of exposure.

When a substance is released from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. This release does not always lead to exposure. You are exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking the substance or by skin contact.

If you are exposed to cyanide, many factors determine whether you'll be harmed. These factors include the dose (how much), the duration (how long), and how you come in contact with it. You must also consider the other chemicals you're exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

1.1 WHAT IS CYANIDE?

Cyanide is usually found in compounds (substances formed by joining two or more chemicals). Cyanide can interact with metals and other organic compounds (compounds that include carbon). Sodium cyanide and potassium cyanide are examples of simple cyanide compounds. Cyanide can be produced by certain bacteria, fungi, and algae, and is found in a number of foods and plants. In your body, cyanide can combine with a chemical (hydroxocobalamin) to form vitamin B_{12} (cyanocobalamin). In certain plant foods, including almonds, millet sprouts, lima beans,

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soy, spinach, bamboo shoots and cassava roots (potato-like tubers of cassava plants grown in the tropics and known in the United States as tapioca), and in vitamin B_{12} cyanide occurs as part of naturally occurring sugars or other complex organic compounds.

Cyanide is a powerful and rapid-acting poison. Hydrogen cyanide has been used in gas-chamber executions and as a war gas.

Much of the cyanide in soil and water comes from industrial processes. The major sources of cyanide in water are discharges from some metal mining processes, organic chemical industries, iron and steel works, and publicly owned waste water treatment works. Other cyanide sources include vehicle exhaust, releases from certain chemical industries, municipal waste burning, and use of cyanide-containing pesticides. Much smaller amounts of cyanide may enter water through storm water runoff in locations where road salts that contain cyanide are used. Underground water can be contaminated by cyanide present in landfills. Hydrogen cyanide, sodium cyanide, and potassium cyanide are the forms of cyanide most likely to be in the environment as a result of industrial activities. Hydrogen cyanide is a colorless gas with a faint, bitter, almond-like odor. Sodium cyanide and potassium cyanide are both white solids with a slight, bitter, almond-like odor in damp air. Cyanide salts and hydrogen cyanide are used in electroplating, metallurgy, organic chemicals production, photographic developing, making plastics, fumigating ships, and some mining processes. Chlorination of water contaminated with cyanide produces the compound cyanogen chloride. Two incidents of cyanide in soil resulted from disposal of cyanide-containing wastes in landfills and use of cyanide-containing road salts. See Chapters 3 and 4 for more information on physical and chemical properties and on production and use of cyanide.

Thiocyanates are a group of compounds formed when sulfur, carbon, and nitrogen are combined. Thiocyanates are found in various foods and plants; however, they are produced primarily from the reaction of free cyanide with sulfur. This reaction occurs in the environment (for example, in industrial waste streams that contain cyanide) and in the human body after swallowing or absorbing cyanide.

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Ammonium thiocyanate is used as an ingredient in antibiotic preparations, pesticides, liquid rocket fuels, adhesives, and matches. It is also used in photographic processes, to improve the strength of silks, and as a weed killer.

Thiocyanates are present in water primarily because of discharges from coal processing, extraction of gold and silver, and mining industries. Thiocyanates in soil result from direct application of weed killers and disposal of by-products from industrial processes. Less important sources include release from damaged or decaying tissues of certain plants such as mustard, kale, and cabbage.

1.2 WHAT HAPPENS TO CYANIDE WHEN IT ENTERS THE ENVIRONMENT?

Cyanide enters air, water, and soil as a result of both natural processes and industrial activities. Airborne cyanide is generally far below levels that would cause concern. In air, cyanide is present mainly as gaseous hydrogen cyanide. A small amount of cyanide in air is present as fine dust particles. This dust eventually settles over land and water. Rain and snow help remove cyanide particles from air. The gaseous hydrogen cyanide is not easily removed from the air by settling, rain, or snow. The half-life (the time needed for half the material to be removed) of hydrogen cyanide in the atmosphere is about 1 to 3 years. Most cyanide in surface water will form hydrogen cyanide and evaporate. Some cyanide in water will be transformed into less harmful chemicals by microorganisms (plants and animals of very small size), or will form a complex with metals, such as iron. The half-life of cyanide in water is not known. Cyanide in water does not build up in the bodies of fish.

Cyanide in soil can form hydrogen cyanide and evaporate. Some of the cyanide will be transformed into other chemical forms by microorganisms in soil. Some forms of cyanide remain in soil, but cyanide usually does not seep into underground water. However, cyanide has been detected in underground waters of a few landfills. At the high concentrations found in some landfill leachates (water that seeps through landfill soil), cyanide becomes toxic to soil microorganisms. Since these microorganisms can no longer change cyanide to other chemical

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forms, cyanide is able to pass through soil into underground water. See Chapters 4 and 5 for more information about what happens to cyanide in the environment.

Less is known about what happens to thiocyanates when they enter the environment. In soil and water, thiocyanates are changed into other chemical forms by microorganisms. At near normal temperatures (30 °C), evaporation or sorption (binding to soil) does not seem to be important for thiocyanates in soil.

See Chapters 4 and 5 for more information about what happens to thiocyanates in the environment.

1.3 HOW MIGHT I BE EXPOSED TO CYANIDE?

You may be exposed to cyanide by breathing air and drinking water, touching soil or water containing cyanide, or eating foods that contain cyanide. Many plant materials, such as cassava roots, lima beans, and almonds, naturally contain low-to-moderate levels of cyanide. The concentration of hydrogen cyanide in unpolluted air is less than 0.0002 parts per million (ppm; 1 ppm is equivalent to 1 part by volume of hydrogen cyanide in a million parts by volume of air). Cyanogen chloride, which might be formed in the process of water chlorination, has been found at concentrations ranging from 0.00045 to 0.0008 ppm (1 ppm is equivalent to 1 part by weight in a million parts by volume of water) in drinking water from 35 United States cities. We do not know how many people in the general population of the United States are exposed to significant amounts of cyanide from eating foods that naturally contain cyanide. Smoking is probably one of the major sources of cyanide exposure for people who do not work in cyanide related industries. Breathing smoke-filled air during fires may also be a major source of cyanide exposure. People who live near hazardous waste sites that contain cyanide may also be exposed to higher amounts of cyanide compared with the general population.

Cyanide is used or produced in various occupational settings where activities include electroplating, some metal mining processes, metallurgy, metal cleaning, certain pesticide applications, tanning, photography and photoengraving, firefighting, and gas works operations.

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Cyanide is also used in some dye and pharmaceutical industries. The National Occupational Exposure Survey (NOES) has estimated the numbers of workers who are potentially exposed to the following forms of cyanide: 4,005 to hydrogen cyanide; 66,493 to sodium cyanide; 64,244 to potassium cyanide; 3,215 to potassium silver cyanide; 3,606 to calcium cyanide; 22,339 to copper (I) cyanide; and 1,393 to cyanogen chloride. See Chapter 5 for more information on exposure to cyanide.

You can be exposed to thiocyanate in the same ways that you may be exposed to cyanide. Exposure to cyanide will also expose you to thiocyanate because cyanide is changed to thiocyanate in your body. Many foods (plants, dairy products, meat) contain thiocyanate. People who work in cyanide-related industries such as the manufacture of electronic computing equipment, commercial printing, photographic processes, hospitals, production of adhesives, and construction and furniture manufacture may be exposed to thiocyanate. No information is available on the concentrations of thiocyanate in unpolluted air or drinking water. We do not know how many people in the general United States population are exposed to significant amounts of thiocyanate from eating foods that contain thiocyanate. People who smoke or breathe tobacco smoke in the environment, and fetuses of mothers exposed to environmental tobacco smoke, may be exposed to high levels of thiocyanate. People who live near hazardous waste sites that contain thiocyanate may potentially be exposed to higher amounts of thiocyanate than the general population. The NOES estimates that a total of 90,599 workers are potentially exposed to ammonium thiocyanate.

1.4 HOW CAN CYANIDE ENTER AND LEAVE MY BODY?

Cyanide can enter your body if you breathe air, eat food, or drink water that contains cyanide. Cyanide can enter your body through the skin, but this is common only for people who work in cyanide-related industries. Exposure to contaminated water, air, or soil can occur at hazardous waste sites. Once it is in your body, cyanide can quickly enter the bloodstream. Some of the cyanide is changed to thiocyanate, which is less harmful, and leaves the body in the urine. Some of the cyanide that enters your body can also combine with hydroxocobalamin to form vitamin B_{12}. A small amount of cyanide is converted in the body to carbon dioxide, which leaves the

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body in the breath. Most of the cyanide and its products leave the body within the first 24 hours after exposure. The way cyanide enters and leaves the body is similar in people and animals. You can find more information about the movement of cyanide in the body in Chapter 2.

1.5 HOW CAN CYANIDE AFFECT MY HEALTH?

To protect the public from the harmful effects of toxic chemicals and to find ways to treat people who have been harmed, scientists use many tests.

One way to see if a chemical will hurt people is to learn how the chemical is absorbed, used, and released by the body; for some chemicals, animal testing may be necessary. Animal testing may also be used to identify health effects such as cancer or birth defects. Without laboratory animals, scientists would lose a basic method to get information needed to make wise decisions to protect public health. Scientists have the responsibility to treat research animals with care and compassion. Laws today protect the welfare of research animals and scientists must comply with strict animal care guidelines.

Exposure to large amounts of cyanide can be deadly. The severity of the harmful effects depends in part on the form of cyanide, such as hydrogen cyanide gas or cyanide salts. Exposure to high levels of cyanide for a short time harms the brain and heart, and can even cause coma and death. People who breathed 546 ppm of hydrogen cyanide have died after a 10-minute exposure; 110 ppm of hydrogen cyanide was life-threatening after a 1 -hour exposure. People who eat large amounts of cyanide in a short time may die. Some of the first indications of cyanide poisoning are rapid, deep breathing and shortness of breath, followed by convulsions and loss of consciousness. These symptoms can occur rapidly, depending on the amount eaten. The health effects of large amounts of cyanide are similar, whether it is eaten, drunk, breathed, or touched. Skin contact with hydrogen cyanide or cyanide salts can irritate and produce sores. Workers who breathed in amounts of hydrogen cyanide as low as 6 to 10 ppm over a period of years had breathing difficulties, pain in the heart area, vomiting, blood changes, headaches, and enlargement of the thyroid gland.

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Use of cassava roots as a primary food source has led to high blood cyanide levels in some people in tropical countries. Some of them suffered harmful effects to the nervous system, including weakness of the fingers and toes, difficulty walking, dimness of vision, and deafness, but chemicals other than cyanide may have also contributed to these effects. Cyanide exposure from cassava was also linked to decreased thyroid gland function and goiter development. These effects have not been seen at levels of cyanide exposure usually found in foods in the United States; however, some children who ate large quantities of apricot pits, which naturally contain cyanide as part of complex sugars, had rapid breathing, low blood pressure, headaches, and coma, and some died. There are no reports that cyanide can directly cause birth defects or reproductive problems in people. However, birth defects were seen in rats that ate cassava root diets, and adverse effects on the reproductive system were seen in rats and mice that drank water containing sodium cyanide. Other cyanide effects in animal studies were similar to those observed in people. There are no reports that cyanide can cause cancer in people or animals. EPA has determined that cyanide is not classifiable as to its human carcinogenicity (ability to cause cancer).

Vitamin B_{12} is a chemical substance containing cyanide that is beneficial to your body because it prevents anemia (iron-poor blood). The cyanide is bound in Vitamin B_{12} so that it does not serve as a source of cyanide exposure and cannot harm you. You can find more information on the harmful effects of cyanide in Chapter 2.

1.6 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO CYANIDE?

Blood and urine levels of cyanide and thiocyanate can be measured, and small amounts of these compounds are always detectable in blood and urine. We do not know the exact cyanide exposure levels linked with high levels of cyanide or thiocyanate in body fluids. Harmful effects can occur when blood levels of cyanide are higher than 0.2 parts per billion (ppb), but some effects may happen at lower levels. Tissue levels of cyanide can be measured if cyanide poisoning is suspected. However, cyanide and thiocyanate are rapidly cleared from the body; therefore, blood measurements can only indicate evidence of recent exposure. A bitter, almond-

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like odor in the breath may alert a physician that a person was exposed to cyanide. For more
information on the health effects of cyanide and how it can be detected in the environment, read
Chapters 2 and 6.

1.7 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The federal government develops regulations and recommendations to protect public health.
Regulations <u>can</u> be enforced by law. Federal agencies that develop regulations for toxic
substances include the Environmental Protection Agency (EPA), the Occupational Safety and
Health Administration (OSHA), and the Food and Drug Administration (FDA).
Recommendations provide valuable guidelines to protect public health but <u>cannot</u> be enforced by
law. Federal organizations that develop recommendations for toxic substances include the
Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for
Occupational Safety and Health (NIOSH).

Regulations and recommendations can be expressed in not-to-exceed levels in air, water, soil, or
food that are usually based on levels that affect animals, then are adjusted to help protect people.
Sometimes these not-to-exceed levels differ among federal organizations because of different
exposure times (an 8-hour workday or a 24-hour day), the use of different animal studies, or
other factors.

Recommendations and regulations are also periodically updated as more information becomes
available. For the most current information, check with the federal agency or organization that
provides it. Some regulations and recommendations for cyanide include the following:
EPA sets rules for the amount of cyanide allowed in drinking water. The highest amount
allowed is 200 micrograms of cyanide per liter of water (µg/L). EPA also sets limits for
amounts of hydrogen cyanide in stored foods that have been treated with cyanide to control
pests. Amounts allowed range from 5 ppm in cucumbers, lettuce, radishes, and tomatoes, to 250
ppm in spices. EPA also requires industries to report spills of 1 pound or more of potassium

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silver cyanide and 10 pounds or more of hydrogen cyanide, potassium cyanide, sodium cyanide, calcium cyanide, or copper cyanide.

OSHA sets levels of cyanide that are allowable in workplace air. The permissible exposure limit (PEL) for cyanide salts is 5 milligrams of cyanide per cubic meter of air (mg/m^3) averaged over an 8-hour workday and 40-hour workweek. NIOSH sets guidelines for chemicals in workplace air. Their recommended exposure limit REL) for workers for 10 minutes is 5 mg/m^3 for calcium cyanide, hydrogen cyanide, potassium cyanide, and sodium cyanide.

For more information on regulations and advisories for cyanide in the environment or workplace, read Chapter 7.

1.8 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department or

> Agency for Toxic Substances and Disease Registry
> Division of Toxicology
> 1600 Clifton Road NE, Mailstop E-29
> Atlanta, GA 30333

* Information line and technical assistance

> Phone: (404) 639-6000
> Fax: (404) 639-6315

ATSDR can also tell you the location of occupational and environmental health clinics. These clinics specialize in recognizing, evaluating, and treating illnesses resulting from exposure to hazardous substances.

* To order toxicological profiles contact

> National Technical Information Service
> 5285 Port Royal Road
> Springfield, VA 22161
> Phone: (800) 553-6847 or (703) 487-4650

2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and
other interested individuals and groups with an overall perspective of the toxicology of cyanide. It
contains descriptions and evaluations of toxicological studies and epidemiological investigations and
provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.
A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near
hazardous waste sites, the information in this section is organized first by route of exposure-inhalation,
oral, and dermal; and then by health effect-death, systemic, immunological, neurological, reproductive,
developmental, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure
periods-acute (14 days or less), intermediate (15-364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures.
The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed adverse-
effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELS
have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure
in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death).
"Less serious" effects are those that are not expected to cause significant dysfunction or death, or those
whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable
amount of judgment may be required in establishing whether an end point should be classified as a
NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient
data to decide whether the effect is indicative of significant dysfunction. However, the Agency has
established guidelines and policies that are used to classify these end points. ATSDR believes that there is
sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and
"serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be
important because it helps the users of the profiles to identify levels of exposure at which major health

effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAEL) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for cyanide. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990a), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

This section provides information regarding known health effects of cyanide exposure. Exposure to hydrogen cyanide (HCN) gas is most common by inhalation. In the discussion below, inhalation exposures are expressed as ppm hydrogen cyanide. Exposure to cyanide can also occur by inhalation of cyanogen gas, a dimer of cyanide. However, cyanogen breaks down in aqueous solution into cyanide ion (CN^{-1}) and OCN^- ions (Cotton and Wilkinson 1980). The rate of the breakdown depends on pH and is faster in basic media (e.g., hydrogen cyanide is in equilibrium as H^+ and CN^- in blood with a pH of

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7.38-7.44) than in acidic media (e.g., hydrogen cyanide is the only species in stomach contents at a pH of 3). The amount of cyanide ion formed within a body tissue or fluid as a result of exposure to cyanogen has been reported; however, the amount varies with type of body tissue and fluid. Thus, it is difficult to estimate cyanide levels in body tissues after cyanogen exposure. Therefore, studies regarding exposure to cyanogen are discussed in the text as ppm cyanogen, but are not included in Levels of Significant Exposure tables or figures.

Oral exposure to cyanide usually results from accidental, homicidal, or suicidal ingestion of cyanide salts. Sodium cyanide and potassium cyanide are the most frequently studied cyanide compounds. Copper cyanide, potassium silver cyanide, silver cyanide, and calcium cyanide are other compounds that humans could encounter through oral or dermal exposure. Cassava roots and certain fruit pits contain compounds that can be broken down to form cyanide. Cassava roots form the staple diet of some populations in Africa, Central and South America, and Asia. However, it must be noted that cassava roots are notoriously deficient in protein and other nutrients and contain many other compounds, in addition to cyanide, that could be responsible for some of the observed toxic effects. Thiocyanate is a metabolite of cyanide that is formed in the body after exposure to cyanide compounds. When possible, all oral exposures are expressed as mg CN⁻/kg/day.

A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

2.2.1 Inhalation Exposure

2.2.1.1 Death

Inhalation of sufficient concentrations of hydrogen cyanide gas can rapidly cause death, which has led to the use of hydrogen cyanide in gas chamber executions (Wexler et al. 1947). An average fatal concentration for humans was estimated as 546 ppm hydrogen cyanide (524 ppm cyanide) after a lo-minute exposure (McNamara 1976, as cited in Ballantyne 1987). In one case, a worker exposed to 200 ppm hydrogen cyanide (192 ppm cyanide) in a silver plating tank became unconscious and eventually died even though he had received antidotal therapy in a hospital (Singh et al. 1989). In other cases, exposure to 270 ppm hydrogen cyanide (259 ppm cyanide) led immediately to death, 18 1 ppm hydrogen cyanide exposure (174 ppm cyanide) was fatal after 10 minutes, and 135 ppm hydrogen cyanide (130 ppm cyanide) after 30 minutes in humans (Dudley et al. 1942).

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Levels of acute exposure resulting in animal deaths were reported in numerous studies and LC_{50} (lethal concentration, 50% death) values were provided for several species. Inhalation LC_{50} values of hydrogen cyanide in rats ranged from 143 ppm (137 ppm cyanide) for 60 minutes to 3,417 ppm (3,280 ppm cyanide) for 10 seconds (Ballantyne 1983a). Exposure to cyanide resulted in similar LC_{50} values in mice (Higgins et al. 1972; Matijak-Schaper and Alarie 1982). LC_{50} values for hydrogen cyanide in rabbits ranged from 188 ppm (18 1 ppm cyanide) for 30 minutes to 2,200 ppm (2,112 ppm cyanide) for 45 seconds (Ballantyne 1983a). Lethal concentrations were also reported in experiments with dogs exposed for acute (Haymaker et al. 1952) and intermediate durations (Valade 1952). Both studies used a small number of dogs for different exposure regimens so that statistical significance could not be evaluated.

The LC_{50} values in each species and LOAEL values for death in humans in the acute-, and intermediate duration category are recorded in Table 2-l and plotted in Figure 2-l.

2.2.1.2 Systemic Effects

The systemic effects observed in humans and animals after inhalation exposure to cyanide are discussed below. The highest NOAEL values and all reliable LOAEL values for each systemic effect in each species and duration category are recorded in Table 2- 1 and plotted in Figure 2- 1.

Respiratory Effects. Initially, respiration is stimulated, but later dyspnea occurs in patients admitted to a hospital after acute hydrogen cyanide exposure (Chen and Rose 1952; Peden et al. 1986; Potter 1950). The levels of exposure in these accidental poisonings were not provided. Nasal irritation was reported in volunteers exposed to 16 ppm cyanogen (8 ppm cyanide) for 6-8 minutes (McNerney and Schrenk 1960). No effects were reported at 8 ppm cyanogen (4 ppm cyanide).

Dyspnea was observed in workers chronically exposed (5-15 years) to 6.4-10.4 ppm of an unspecified cyanide form evolved from sodium cyanide and copper cyanide during electroplating (El Ghawabi et al. 1975) and in workers exposed to 15 ppm hydrogen cyanide (14 ppm cyanide) in a silver-reclaiming facility (Blanc et al. 1985). Other complaints included cough, sore throat, altered sense of smell, nasal congestion, epistaxis, and hemoptysis. However, exposure to other chemicals such as cleaners and cutting oils also occurs in electroplating operations.

Table 2-1. Levels of Significant Exposure to Cyanide - Inhalation

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
ACUTE EXPOSURE							
Death							
1	Human	10 min				524 (LC$_{50}$)	McNamara 1976 HCN
2	Human	NS				192 M (fatal after 3 days)	Singh et al. 1989 HCN
3	Rat (NS)	60 min				137 (LC$_{50}$ in 60 min)	Ballantyne 1983a HCN
4	Rat (Wistar)	5 min				483 (LC$_{50}$)	Higgins et al. 1972 HCN
5	Mouse (ICR)	5 min				310 (LC$_{50}$)	Higgins et al. 1972 HCN
6	Mouse (ICR)	3 min				400 M (90% lethality)	Hume et al. 1995 HCN
7	Mouse (Swiss-Webster)	30 min				159 M (LC$_{50}$)	Matijak-Schaper and Alarie 1982 HCN
8	Rabbit (NS)	35 min				181 (LC$_{50}$ in 35 min)	Ballantyne 1983a HCN
Systemic							
9	Human	13 min	Ocular		434 M (slight loss of peripheral vision after recovery)		Bonsall 1984 HCN
10	Monkey (Cyno-molgus)	30 min	Resp			96 (severe dyspnea)	Purser et al. 1984 HCN
			Cardio			96 (bradycardia, arrhythmia, T-wave abnormalities)	

Table 2-1. Levels of Significant Exposure to Cyanide - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL		Reference Chemical Form
					Less serious (ppm)	Serious (ppm)	
11	Mouse (Swiss-Webster)	30 min	Resp			60 M (DC$_{50}$)	Matijak-Schaper and Alarie 1982 HCN
Neurological							
12	Human	13 min				434 M (coma)	Bonsall 1984 HCN
13	Monkey (Cyno-molgus)	30 min				96 (semiconsciousness, disrupted respiration, EEG changes)	Purser et al. 1984 HCN
INTERMEDIATE EXPOSURE							
Death							
14	Dog (NS)	28 d 2-day intervals 30 min/d				43 (1/4 died)	Valade 1952 HCN
Systemic							
15	Rat (Long- Evans)	5 x/20 d 4 d intervals 12.5 min/x	Cardio			192 M (increased creatine phosphokinase activity)	O'Flaherty and Thomas 1982 HCN
16	Dog (NS)	28 d 2-day intervals 30 min/d	Resp Gastro		43 (vomiting, tenesmus, and diarrhea)	43 (dyspnea)	Valade 1952 HCN

Table 2-1. Levels of Significant Exposure to Cyanide - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
Neurological							
17	Dog (NS)	28 d 2-day intervals 30 min/d				43 (tremors, stiffness, ataxia, vasodilation and hemmorhage, atrophy of Purkinje and glial cells)	Valade 1952 HCN
CHRONIC EXPOSURE							
Systemic							
18	Human	NS	Resp		14 M (dyspnea)		Blanc et al. 1985 HCN
			Cardio		14 M (palpitations, chest pain)		
			Gastro		14 M (nausea)		
			Endocr		14 M (increased mean thyroid stimulating hormone levels)		
			Dermal		14 M (rash)		
			Ocular		14 M (eye irritation)		
			Bd Wt		14 M (approximately 8% weight loss)		

Table 2-1. Levels of Significant Exposure to Cyanide - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL		Reference Chemical Form
					Less serious (ppm)	Serious (ppm)	
19	Human	5-15 yr (occup)	Resp		6.4 M (dyspnea, irritation of throat)		El Ghawabi et al. 1975 NaCN
			Cardio		6.4 M (precordial pain)		
			Gastro		6.4 M (vomiting)		
			Hemato		6.4 M (increased hemoglobin and lymphocytes)		
			Endocr		6.4 M (thyroid enlargement)		
			Dermal	10.4 M			
			Ocular		6.4 M (lacrimation)		
Neurological							
20	Human	NS				14 M (persistent headache, dizziness, paresthesia)	Blanc et al. 1985 HCN
21	Human	5-15 yr (occup)				6.4 M (confusion, hallucination, headache, dizziness, weakness)	El Ghawabi et al. 1975 NaCN

[a]The number corresponds to entries on Figure 2-1.

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); DC_{50} = concentration that resulted in 50% decrease in average respiratory rate; EEG = electroencephalogram; Endocr = endocrine; F = female; Gastro = gastrointestinal; HCN = hydrogen cyanide; Hemato = hematological; LC_{50} = lethal concentration, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; min = minutes; NaCN = sodium cyanide; NOAEL = no-observed-adverse-effect level; NS = not specified; (occup) = occupational; Resp = respiratory; sec = second(s); yr = year(s); x = time(s)

Figure 2-1. Levels of Significant Exposure to Cyanide - Inhalation
Acute (≤14 days)

Key

r	rat	■ LC$_{50}$ (animals)	The number next to each point corresponds to entries in Table 2-1.
m	mouse	● LOAEL for serious effects (animals)	
h	rabbit	◐ LOAEL for less serious effects (animals)	
d	dog	◆ CEL: cancer effect level (animals)	
k	monkey	▲ LOAEL for serious effects (humans)	
		▲ LOAEL for less serious effects (humans)	
		△ NOAEL (humans)	

Figure 2-1. Levels of Significant Exposure to Cyanide - Inhalation (cont.)

Intermediate (15-364 days)

Key

r rat	■ LC$_{50}$ (animals)	The number next to each point corresponds to entries in Table 2-1.
m mouse	● LOAEL for serious effects (animals)	
h rabbit	◑ LOAEL for less serious effects (animals)	
d dog		
k monkey	◆ CEL: cancer effect level (animals)	
	▲ LOAEL for serious effects (humans)	
	▲ LOAEL for less serious effects (humans)	
	△ NOAEL (humans)	

Figure 2-1. Levels of Significant Exposure to Cyanide - Inhalation (cont.)

Chronic (≥365 days)

Systemic

Key

r	rat
m	mouse
h	rabbit
d	dog
k	monkey

■ LC$_{50}$ (animals)

● LOAEL for serious effects (animals)

◖ LOAEL for less serious effects (animals)

◆ CEL: cancer effect level (animals)

▲ LOAEL for serious effects (humans)

▲ LOAEL for less serious effects (humans)

△ NOAEL (humans)

The number next to each point corresponds to entries in Table 2-1.
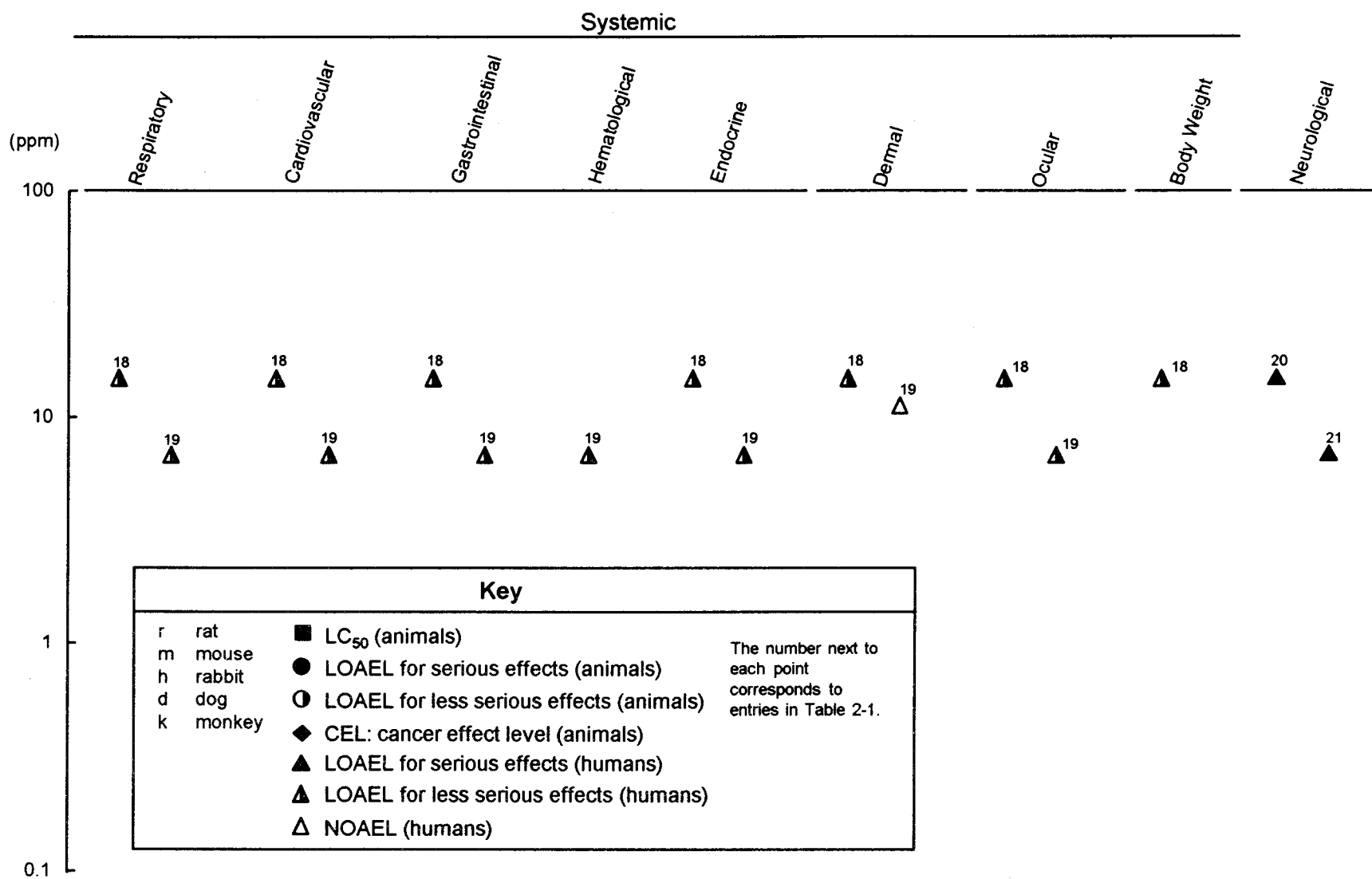
2. HEALTH EFFECTS

Asphyxia has been observed in rats exposed to 250 ppm cyanogen (125 ppm cyanide) for 7.5-120 minutes (McNemey and Schrenk 1960), asphyxia and pulmonary edema were observed in dogs exposed to concentrations ranging from 149 to 633 ppm hydrogen cyanide (143-608 ppm cyanide) for 2-10 minutes (Haymaker et al. 1952), while severe dyspnea was observed in monkeys exposed to 100 ppm hydrogen cyanide (96 ppm cyanide) for 30 minutes (Purser et al. 1984). Exposure to 63 ppm hydrogen cyanide (60 ppm cyanide) for 30 minutes resulted in a 50% decrease in respiratory rate of mice due to depression of the respiratory center (Matijak-Schaper and Alarie 1982).

In intermediate-duration studies, no respiratory effects were reported in rats exposed to 25 ppm cyanogen (50 ppm cyanide) for 6 months, and a decrease in total lung moisture content was the only finding in monkeys exposed to 11 ppm cyanogen (22 ppm cyanide), also for 6 months (Lewis et al. 1984). Dyspnea was found in dogs exposed to 45 ppm hydrogen cyanide (43 ppm cyanide) for 30 minutes a day at 2-8-day intervals for 28-96 days (Valade 1952).

Cardiovascular Effects. Wexler (1947) reported on four men executed by inhalation of hydrogen cyanide gas (concentration not reported). He reported a distinct slowing of the heart rate within l-3 minutes of exposure, with further changes in the heart rate, sinus irregularities, and audio-visual dissociation. Palpitations and hypotension were the most frequently reported cardiovascular effects in patients after accidental inhalation poisoning with cyanide; however, exact exposure levels were not known (Peden et al. 1986). Workers occupationally exposed to 6.4-10.4 ppm cyanide for 5-15 years, which evolved from sodium cyanide and copper cyanide during electroplating, complained of precordial pain (El Ghawabi et al. 1975). About 14% of workers exposed to 15 ppm hydrogen cyanide (14 ppm cyanide) in a silver-reclaiming facility reported palpitations and 3 1% reported chest pain (Blanc et al. 1985). Exposure to other chemicals such as cleaners and cutting oils may have also occurred during electroplating operations.

Bradycardia, arrhythmias, and T-wave abnormalities were observed in monkeys exposed to 100 ppm hydrogen cyanide (96 ppm cyanide) for 30 minutes (Purser et al. 1984). Increased cardiac-specific creatinine phosphokinase activity was measured in blood samples from rats 2 hours after 12.5 minutes of exposure to 200 ppm hydrogen cyanide (192 ppm cyanide) for 20 days at 4-day intervals (O'Flaherty and Thomas 1982). However, no treatment-related changes were found in the hearts at histopathology. In addition, no cardiovascular effects were reported at necropsy in rats and monkeys exposed to 25 ppm cyanogen (50 ppm cyanide) for 6 months (Lewis et al. 1984).

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Gastrointestinal Effects. Nausea or vomiting was reported in 69% of workers exposed to 15 ppm hydrogen cyanide (14 ppm cyanide) in a silver reclaiming facility (Blanc et al. 1985). Vomiting was also reported in workers exposed to 6.4-10.4 ppm cyanide evolved from sodium cyanide and copper cyanide during electroplating (El Ghawabi et al. 1975), but exposure to other chemicals such as cleaners and cutting oils may have also contributed to the effects. The gastrointestinal effects resulting from cyanide exposure are probably provoked by central nervous system effects and/or by irritation of the gastric mucosa in cases in which the gas is swallowed during breathing.

Information regarding gastrointestinal effects in animals is limited to a report of vomiting in dogs exposed to 45 ppm hydrogen cyanide (43 ppm cyanide) for 28-96 days (Valade 1952).

Hematological Effects. Increased hemoglobin and lymphocyte count were observed in workers exposed to 6.4-10.4 ppm of an unspecified cyanide form during electroplating (El Ghawabi et al. 1975). The results were significantly different from controls. Furthermore, punctate basophilia of erythrocytes, which indicated toxic poisoning, was present in 28 of 36 subjects. However, exposure to copper, a known hematotoxic agent, also occurred during the electroplating operations. In another study (Kumar et al. 1992), an increase in neutrophil values, an increase in erythrocyte sedimentation rate, and a decrease in hemoglobin levels were noted in male workers exposed to unspecified concentrations of cyanide for an unspecified duration during case hardening and electroplating.

In animals, no hematological effects were found in rats and monkeys exposed to 25 ppm cyanogen (50 ppm cyanide) 6 hours per day, 5 days per week, for 6 months (Lewis et al. 1984).

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after inhalation exposure to cyanide.

No musculoskeletal effects were observed in rats or monkeys exposed to 25 ppm cyanogen (50 ppm cyanide) for 6 hours per day, 5 days per week for 6 months (Lewis et al. 1984).

Hepatic Effects. An increase in serum alkaline phosphatase was noted in workers exposed to unspecified levels of cyanide; however, serum bilirubin was found to be within the normal range in these workers (Kumar et al. 1992).

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Only one study reported on pathological and histopathological examinations of the liver in animals. No changes were found in rats and monkeys exposed to 25 ppm cyanogen (50 ppm cyanide) for 6 months (Lewis et al. 1984).

Renal Effects. One study was located regarding renal effects in humans after inhalation exposure to cyanide. Singh et al. (1989) reported anuria followed by polyuria in a man who was occupationally exposed to 200 ppm hydrogen cyanide (192 ppm cyanide) for an unspecified length of time. No histopathological changes were observed in kidneys of rats and monkeys exposed to 25 ppm cyanogen (50 ppm cyanide) 6 hours per day, 5 days per week for 6 months (Lewis et al. 1984).

Endocrine Effects. Mean thyroid stimulating hormone (TSH) levels (all exposed workers) were significantly higher (although within normal limits) in workers exposed to 15 ppm hydrogen cyanide (14 ppm cyanide) for an unspecified duration in a silver-reclaiming facility than in unexposed individuals ($P< 0.05$). T_3 levels in high exposure workers were also elevated relative to unexposed workers ($p<0.01$). Data for T_4 were not presented, but the investigators indicated that the absence of T_4 abnormalities could be accounted for by the time lapse between exposure and examination (median 10.5 months) (Blanc et al. 1985). Similarly, thyroid enlargement was present in 20 of 36 workers exposed, for 5-15 years, to 6.4-10.4 ppm cyanide evolved from sodium cyanide and copper cyanide. The endocrine effect may be due to formation of thiocyanate, a metabolite of cyanide. However, exposure to other chemicals such as cleaners and cutting oils also occurs during electroplating operations. Thyroid [131] I uptake was significantly higher when compared with the control group. This may be due to cyanide's ability to block iodine uptake and organification by the thyroid gland. Since the workers were away from work on the 2 days preceding the test, the results may be explained on the basis of acute cyanide withdrawal, as with other anti-thyroid agents, where sudden cessation of the drug leads to rapid accumulation of iodine in the iodine-depleted gland (El Ghawabi et al. 1975).

No studies were located regarding endocrine effects in animals after inhalation exposure to cyanide.

Dermal Effects. Cyanide caused a rash in 42% of workers exposed to 15 ppm hydrogen cyanide (14 ppm cyanide) (Blanc et al. 1985). Brick-red chemical bums on the skin were observed in a man who was occupationally exposed to 200 ppm hydrogen cyanide (192 ppm cyanide) for an unspecified length of time (Singh et al. 1989). No dermatitis was reported in workers exposed to 6.4-10.4 ppm cyanide evolved from sodium cyanide and copper cyanide (El Ghawabi et al. 1975).

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No studies were located regarding dermal effects in animals after inhalation exposure to cyanide.

Ocular Effects. Cyanogen caused eye irritation in volunteers during acute exposure to 16 ppm (8 ppm cyanide) (McNemey and Schrenk 1960). No effect was observed in those exposed to 8 ppm cyanogen (4 ppm cyanide). Slight loss of peripheral vision was the only persistent finding from a case report of a man who had been exposed to 452 ppm hydrogen cyanide (434 ppm cyanide) for 13 minutes while cleaning a chemical tank (Bonsall 1984). During chronic occupational exposure, eye irritation occurred in workers of two electroplating factories (exposure levels not specified) (Chandra et al. 1988). In other studies, cyanide caused eye irritation in 58% of workers exposed to 15 ppm hydrogen cyanide (14 ppm cyanide) (Blanc et al. 1985), and lacrimation in workers exposed to 6.4 ppm cyanide (El Ghawabi et al. 1975). The eye irritation may not be due solely to cyanide exposure, as electroplating workers may be exposed to a variety of chemicals that are irritating to the eyes.

Information regarding ocular effects in animals after inhalation exposure to cyanide is limited to a report of eye irritation in rats acutely exposed (7.5-120 minutes) to 250 ppm cyanogen (500 ppm cyanide) (McNemey and Schrenk 1960).

Body Weight Effects. In an occupational setting, loss of appetite was reported in 58% and weight loss (approximately 8%) in 50% of workers exposed to 15 ppm hydrogen cyanide (14 ppm cyanide) for an unspecified duration in a silver-reclaiming facility (Blanc et al. 1985).

Decreased body weight was reported in rats exposed to 25 ppm cyanogen (50 ppm cyanide) 6 hours a day, 5 days a week for 6 months (Lewis et al. 1984).

2.2.1.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans or animals after inhalation exposure to cyanide.

2.2.1.4 Neurological Effects

The central nervous system is a primary target for cyanide toxicity. Acute exposure of humans to fatal levels of hydrogen cyanide causes a brief stage of central nervous system stimulation followed by depression, convulsions, coma with abolished deep reflexes and dilated pupils, paralysis, and in some

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cases, death (Bonsall 1984; Chen and Rose 1952; Peden et al. 1986; Potter 1950; Singh et al. 1989). Though clinical symptoms of cyanide poisoning are well recognized, specific dose-response data are generally not known. Acute exposure to lower concentrations can cause lightheadedness, breathlessness, dizziness, numbness, and headaches (Peden et al. 1986).

Chronic exposure of humans to potassium cyanide and other chemicals may have produced severe neurological effects such as hemiparesis and hemianopia (Sandberg 1967). During chronic occupational exposure, workers exposed to 15 ppm hydrogen cyanide (14 ppm cyanide) for an unspecified duration reported fatigue, dizziness, headaches, disturbed sleep, ringing in ears, paresthesias of extremities, and syncopes (Blanc et al. 1985). A dose-effect was demonstrated on high- and low-exposure jobs; however, exact cyanide concentrations in the air were not known. Neurological effects persisted in some workers even after a 10-month nonexposure period. Similar effects were observed in workers exposed to 6.4 ppm cyanide (El Ghawabi et al. 1975). Clinical symptoms included headaches, weakness, changes in taste and smell, dizziness, disturbances of accommodation, and psychosis. A recent study (Kumar et al. 1992) reported loss of delayed and immediate memory, and a decrease in visual ability, psychomotor ability, and visual learning in workers exposed to unspecified levels of hydrogen cyanide for an unspecified duration. In another study, chronic occupational exposure of workers (5-19 years) to hydrogen cyanide (exposure levels not specified) resulted in headaches and dizziness in workers (Chandra et al. 1988). Furthermore, when behavioral functions were tested in this cohort, an alteration of delayed memory and/or visual impairment was found in 31.5% of workers. However, exposure to other chemicals, such as cleaners and cutting oils, also occurs during electroplating operations.

The central nervous system is also a primary target for cyanide toxicity in animals. Following acute exposure, neurological effects before death included restless and panic movements, poor coordination, tremor, and lethargy in rats exposed to 250 ppm cyanogen (500 ppm cyanide) for 1.5-120 minutes (McNemey and Schrenk 1960). When rats were exposed to unspecified concentrations of hydrogen cyanide and kept unconscious for 20-60 minutes, lesions of various degrees developed in the brain (Hirano et al. 1967; Levine 1969; Levine and Stypulkowski 1959a). Necrosis was found mainly in the mid-sagittal sections of the brain. Demyelination was also reported and morphological signs indicative of remyelination were reported in rats several months after cyanide intoxication (Hirano et al. 1968), but it was apparent that this process was slow and incomplete. Acute exposure of dogs for 2-10 minutes, each to a different concentration ranging from 149 to 633 ppm hydrogen cyanide (143-608 ppm cyanide), resulted in motor incoordination, muscular rigidity, and coma (Haymaker et al. 1952). Extensive necrosis in the grey matter of the neural system was observed at necropsy. Acute exposure (30 minutes) to

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100 ppm hydrogen cyanide (96 ppm cyanide) induced semiconsciousness rapidly in monkeys (Purser et al. 1984). An increase in delta activity was observed in the electroencephalogram. Cyanide exposure levels in most acute duration studies were relatively high and usually caused death in some animals. OnIy transitory behavioral changes were reported in monkeys exposed to 25 ppm cyanogen (50 ppm cyanide) for 6 months (Lewis et al. 1984). No effects were found at 11 ppm cyanogen (22 ppm cyanide) exposure. Exposure of dogs to 45 ppm hydrogen cyanide (43 ppm cyanide) for 28-96 days caused tremors, convulsions, and coma (Valade 1952). Vascular and cellular lesions were found in the central nervous system.

The highest NOAEL value and all reliable LOAEL values for neurological effects in each species and duration category are recorded in Table 2-l and plotted in Figure 2- 1.

No studies were located regarding the following health effects in humans or animals after inhalation exposure to cyanide:

2.2.1.5 Reproductive Effects

2.2.1.6 Developmental Effects

2.2.1.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.5.

2.2.1.8 Cancer

No studies were located regarding cancer effects in humans or animals after inhalation exposure to cyanide.

2.2.2 Oral Exposure

2.2.2.1 Death

An average fatal dose of 1.52 mg/kg cyanide for humans has been calculated from case report studies of intentional or accidental poisonings (EPA 1987a). The lowest fatal oral dose reported in humans is 0.56 mg/kg cyanide (Gettler and Baine 1938).

Oral LD_{50} (lethal dose, 50% death) values were calculated for rats as 3 mg CN⁻/kg (Ballantyne 1988) or 8 mg CN⁻/kg (Smyth et al. 1969) given as sodium cyanide. An LD_{50} of 2.7 mg CN⁻/kg/day was reported for starved rats (Ballantyne 1988). However, since starvation rendered these animals physiologically compromised, this value should not be considered reliable. An acute LD_{50} of 22 mg CN⁻/kg as calcium cyanide was reported in rats (Smyth et al. 1969). Acute LD_{50} values in rabbits showed little variation (2.34–2.7 mg CN⁻/kg/day) regardless of whether the source was hydrocyanic acid, sodium cyanide, or potassium cyanide (Ballantyne 1983a). High mortality occurred in rats and mice that received a single dose of 4 and 6 mg CN⁻/kg, respectively, in the form of potassium cyanide (Ferguson 1962). Greater dilution of dosages in water resulted in higher mortality. Increased mortality was observed in rats exposed to 14.5 mg CN⁻/kg/day as copper cyanide for 90 days (Gerhart 1987a) and to 2.6 mg CN⁻/kg/day as potassium silver cyanide for 90 days (Gerhart 1987b). Hemolytic anemia, which probably resulted from copper toxicity, caused death in rats exposed to copper cyanide (Gerhart 1987a). No deaths were reported in male and female rats exposed to 0.2–12.5 mg CN⁻/kg/day in the drinking water for 13 weeks (NTP 1993).

When comparing the available acute lethal toxicity information for cyanide compounds, it was concluded that, for oral exposure, the molar lethal toxicities of hydrogen cyanide, sodium cyanide, and potassium cyanide are similar. Rabbits appeared to be more susceptible to the lethal toxicity of these three compounds than rats (Ballantyne 1988).

The LD_{50} and minimum lethal dose (LD_{LO}) values in each species and all reliable LOAEL values for death in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

Table 2-2. Levels of Significant Exposure to Cyanide - Oral

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
ACUTE EXPOSURE							
Death							
1	Rat (Sprague-Dawley)	once (GW)				4 (19/20 died)	Ferguson 1962 KCN
2	Rat (NS)	once (GW)				8 (LD$_{50}$)	Smyth et al. 1969 NaCN
3	Rat (NS)	once (GW)				22 (LD$_{50}$)	Smyth et al. 1969 Ca(CN)2
4	Mouse (Swiss-Webster)	once (GW)				6 (19/20 died)	Ferguson 1962 KCN
Systemic							
5	Human	once (IN)	Resp			15 M (hyperventilation)	Liebowitz and Schwartz 1948 KCN
			Cardio			15 M (shallow pulse, inaudible heart sounds, enlarged heart)	
			Gastro		15M (vomiting and nausea)		
			Hemato	15M			
			Musc/skel		15M (generalized muscular rigidity)		
			Renal			15 M (albuminuria)	

Table 2-2. Levels of Significant Exposure to Cyanide - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
Neurological							
6	Human	once (IN)				15 M (coma)	Liebowitz and Schwartz 1948 KCN
Reproductive							
7	Hamster (Syrian)	Gd 3-14 (F)		10.4 F			Frakes et al. 1986 Cassava
Developmental							
8	Hamster (Syrian)	Gd 3-14 (F)				1.0 (23% decreased fetal weight and delayed ossification)	Frakes et al. 1986 Cassava
INTERMEDIATE EXPOSURE							
Death							
9	Rat (Sprague-Dawley)	90 d 1 x/d (G)				14.5 (23/40)	Gerhart 1987a CuCN
10	Rat (Sprague-Dawley)	90 d 1 x/d (G)				2.6 (9/40 died)	Gerhart 1987b KAg(CN)2

Table 2-2. Levels of Significant Exposure to Cyanide - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL				Reference Chemical Form
					Less Serious (mg/kg/day)		Serious (mg/kg/day)		
Systemic									
11	Rat (Sprague-Dawley)	90 d 1 x/d (G)	Resp	1.45	4.35	(labored respiration, severity not reported)			Gerhart 1987a CuCN
			Dermal		14.5	(discolored inguinal fur)			
			Ocular	14.5					
			Bd Wt	1.45 M	4.35 M	(12% decreased body weight gain)			
12	Rat (Sprague-Dawley)	90 d 1 x/d (G)	Resp		0.8	(labored respiration, severity not reported)			Gerhart 1987b KAg(CN)2
			Cardio	7.8					
			Gastro	7.8					
			Hemato	2.6	7.8	(increased hemoglobin)			
			Hepatic	7.8					
			Renal	2.6	7.8	(increased BUN)			
			Dermal	0.8	2.6	(discolored fur)			
			Ocular	0.8			2.6	(corneal opacity)	
			Bd Wt	0.8 M			2.6 M	(21% decreased body weight gain)	
13	Rat (Fischer- 344)	13 wk (W)	Resp	12.5					NTP 1993 NaCN
			Cardio	12.5					
			Hemato	12.5					
			Hepatic	12.5					
			Renal	12.5					
			Endocr	12.5					
			Bd Wt	12.5					

Table 2-2. Levels of Significant Exposure to Cyanide - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
14	Rat (NS)	11.5 mo (F)	Endocr		30 M (decreased plasma thyroxine at 4 months; increased thyroid weight at 11 months)		Philbrick et al. 1979 KCN
			Bd Wt			30 M (38% decreased weight gain)	
15	Rat (NS)	11.5 mo (F)	Endocr		67 M (decreased plasma thyroxine and thyroxine secreting rate; increased thyroid weight at 11 mo)		Philbrick et al. 1979 KSCN
			Bd Wt	67 M			
16	Mouse (B6C3F1)	13 wk (W)	Cardio	24.3 M 28.8 F			NTP 1993 NaCN
			Hemato	24.3 M 28.8 F			
			Hepatic	24.3 M 28.8 F			
			Renal	24.3 M 28.8 F			
			Endocr	24.3 M 28.8 F			
			Bd Wt	24.3 M 28.8 F			

Table 2-2. Levels of Significant Exposure to Cyanide - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
17	Dog (NS)	14 wk (F)	Cardio			1.04 M (hemorrhage, pyknotic nuclei and swelling of muscle fibers)	Kamalu 1993 Cassava
			Hepatic		1.04 M (periportal vacuolation and congestion)		
			Renal			1.04 M (increased urinary protein, congested kidneys with vacuolation, casts, desquamation, and proximal tubule damage)	
			Endocr			1.04 M (adrenal cortex swelling, hemorrhage, and fibrosis)	
			Metabolic		1.04 M (decreased albumin, Ca & K levels)		
18	Dog (NS)	14 wk (F)	Cardio	1.04 M			Kamalu 1993 NaCN
			Hepatic	1.04 M			
			Renal			1.04 M (increased urinary protein, casts and some desquamation)	
			Endocr		1.04 M (thickening of zona glomerulosa)		
			Metabolic		1.04 M (decreased albumin and K levels)		
19	Pig (Pittman-Moore)	24 wk 7 d/wk 1 x/d (GW)	Gastro	0.4	0.7 (vomiting)		Jackson 1988 KCN
			Endocr		0.4 (T3 and T4 depression)		

Table 2-2. Levels of Significant Exposure to Cyanide - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
20	Pig (Yorkshire)	Gd 1-110 (F)	Renal		0.64 F (proliferation of glomerular cells in dams)		Tewe and Maner 1981b KCN & cassava
			Endocr	5.6 F	11.3 F (thyroid gland hypofunction and enlargement in dams)		

Immunological/Lymphoreticular

| 21 | Rat (Fischer-344) | 13 wk (W) | | 12.5 | | | NTP 1993 NaCN |
| 22 | Mouse (B6C3F1) | 13 wk (W) | | 24.3 M 28.8 F | | | NTP 1993 NaCN |

Neurological

23	Rat (Sprague-Dawley)	90 d 1 x/d (G)			0.14 (hypoactivity and posture hunching)		Gerhart 1987a CuCN
24	Rat (Sprague-Dawley)	90 d 1 x/d (G)			0.8 (hypoactivity)	7.8 (convulsions, lethargy)	Gerhart 1987b KAg(CN)2
25	Rat (Fischer-344)	13 wk (W)		12.5			NTP 1993 NaCN
26	Rat (NS)	11.5 mo (F)				30 M (modest myelin degeneration in spinal cord)	Philbrick et al. 1979 KCN
27	Rat (NS)	11.5 mo (F)				67 M (modest myelin degeneration in spinal cord)	Philbrick et al. 1979 KSCN

Table 2-2. Levels of Significant Exposure to Cyanide - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
28	Mouse (B6C3F1)	13 wk (W)		24.3 M 28.8 F			NTP 1993 NaCN
29	Pig (Pittman-Moore)	24 wk 7 d/wk 1 x/d (GW)			0.4 (reduced exploratory, increased victimization behavior)		Jackson 1988 KCN
Reproductive							
30	Rat (Sprague-Dawley)	90 d 1 x/d (G)		4.35	14.5 (increased testes weight)		Gerhart 1987a CuCN
31	Rat (Sprague-Dawley)	90 d 1 x/d (G)		0.8	2.6 (increased gonadal weight in males)		Gerhart 1987b KAg(CN)2
32	Rat (Fischer- 344)	13 wk (W)		4.5 [b] M 12.5 F	12.5 M (decreased left epididymal (7%), left caudal epididymal (13%), & testes weights (8%), number of spermatid heads per testis (14%), & spermatid count (14%))		NTP 1993 NaCN
33	Mouse (B6C3F1)	13 wk (W)		8.6 M 28.8 F	24.3 M (10 and 18% decrease in left epididymus and caudal epididymus weights)		NTP 1993 NaCN

Table 2-2. Levels of Significant Exposure to Cyanide - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
33	Mouse (B6C3F1)	13 wk (W)		8.6 M	24.3 M (10 and 18% decrease in left epididymus and caudal epididymus weights)		NTP 1993 NaCN
				28.8 F			
34	Dog (NS)	14 wk (F)				1.04 M (reduced spermatogenesis cycle, germ cell sloughing and degeneration)	Kamalu 1993 NaCN
35	Dog (NS)	14 wk (F)				1.04 M (occasional abnormal cells and seminiferous tubules devoid of normal germ cells)	Kamalu 1993 Cassava
Developmental							
36	Rat (Wistar)	Gd 1-16 or 1-20 Ld 1-21 (F)		1.2	51 (decreased growth in pups)		Tewe and Maner 1981a KCN

[a] The number corresponds to entries on Figure 2-2.

[b] Used to derive intermediate oral minimal risk level (MRL) of 0.05 mg/kg/day; dose divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans, and 10 for human variability).

Bd Wt = body weight; BUN = blood urea nitrogen; Cardio = cardiovascular; CA(CN)$_2$ = calcium cyanide; CN = cyanide ion; CuCN = copper cyanide; d = day(s); Endocr = endocrine; F = female; (F) = feed; (G) = gavage; Gastro = gastrointestinal; Gd = gestational day; (GW) = gavage in water; HCN = hydrogen cyanide; Hemato = hematological; incr = increased; KAgCN$_2$ = potassium silver cyanide; KCN = potassium cyanide; KSCN = potassium thiocyanate; Ld = lactation day; LD$_{50}$ = lethal dose, 50% kill; LD$_{LO}$ = lowest lethal dose; LOAEL = lowest-observed-adverse-effect level; M = male; mo = month(s); NaCN = sodium cyanide; NOAEL = no-observed-adverse-effect level; NS = not specified; NTP = National Toxicology Program; Resp = respiratory; SDH = sorbital dehydrogenase; (W) = water; wk = week(s); x = times

Figure 2-2. Levels of Significant Exposure to Cyanide - Oral

Acute (≤14 days)

Key

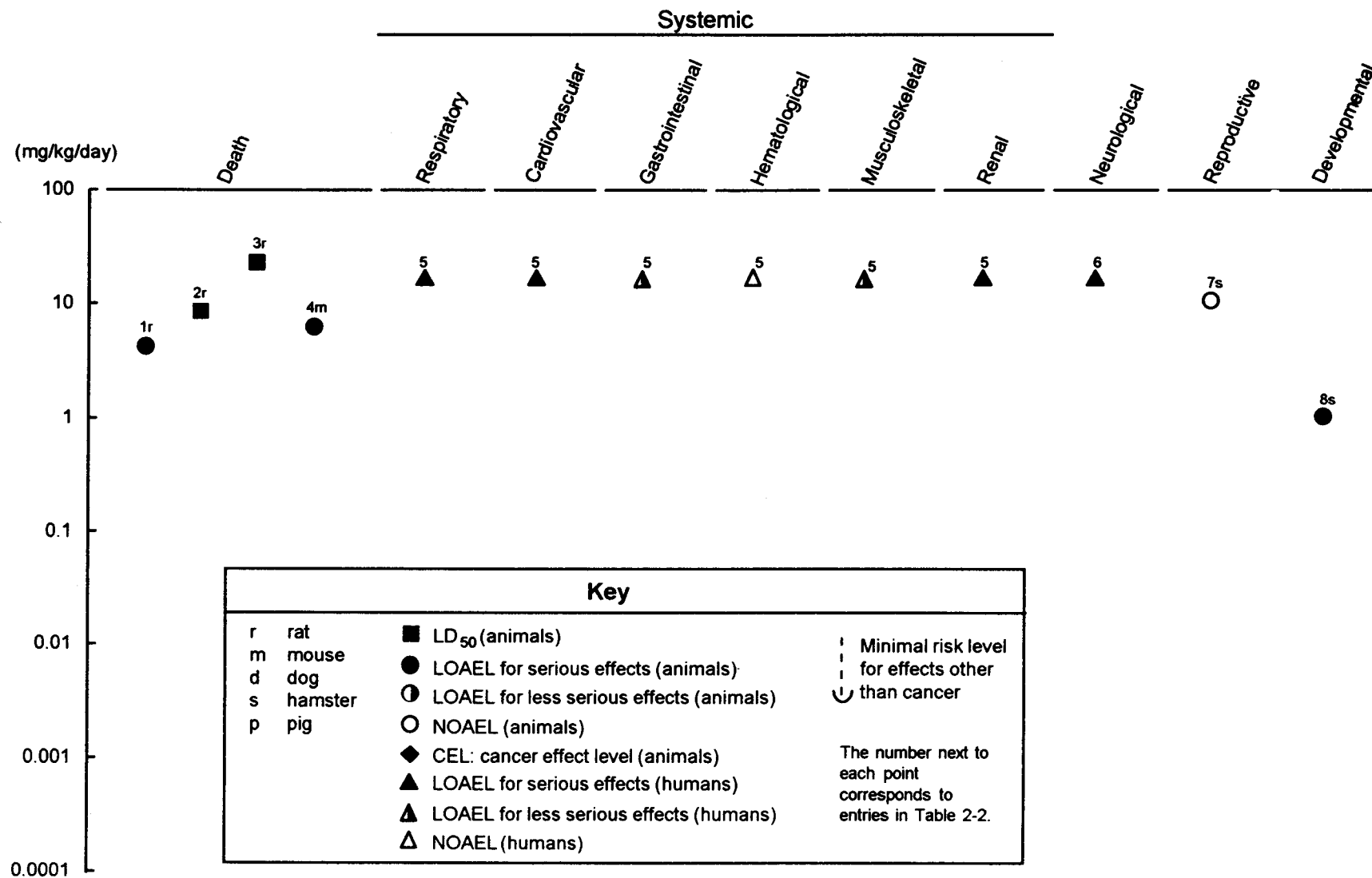|					
r	rat	■	LD_{50} (animals)	¦	Minimal risk level
m	mouse	●	LOAEL for serious effects (animals)	¦	for effects other
d	dog	◑	LOAEL for less serious effects (animals)	∪	than cancer
s	hamster	○	NOAEL (animals)		
p	pig	◆	CEL: cancer effect level (animals)	The number next to	
		▲	LOAEL for serious effects (humans)	each point	
		▲	LOAEL for less serious effects (humans)	corresponds to	
		△	NOAEL (humans)	entries in Table 2-2.	

Figure 2-2. Levels of Significant Exposure to Cyanide - Oral (cont.)

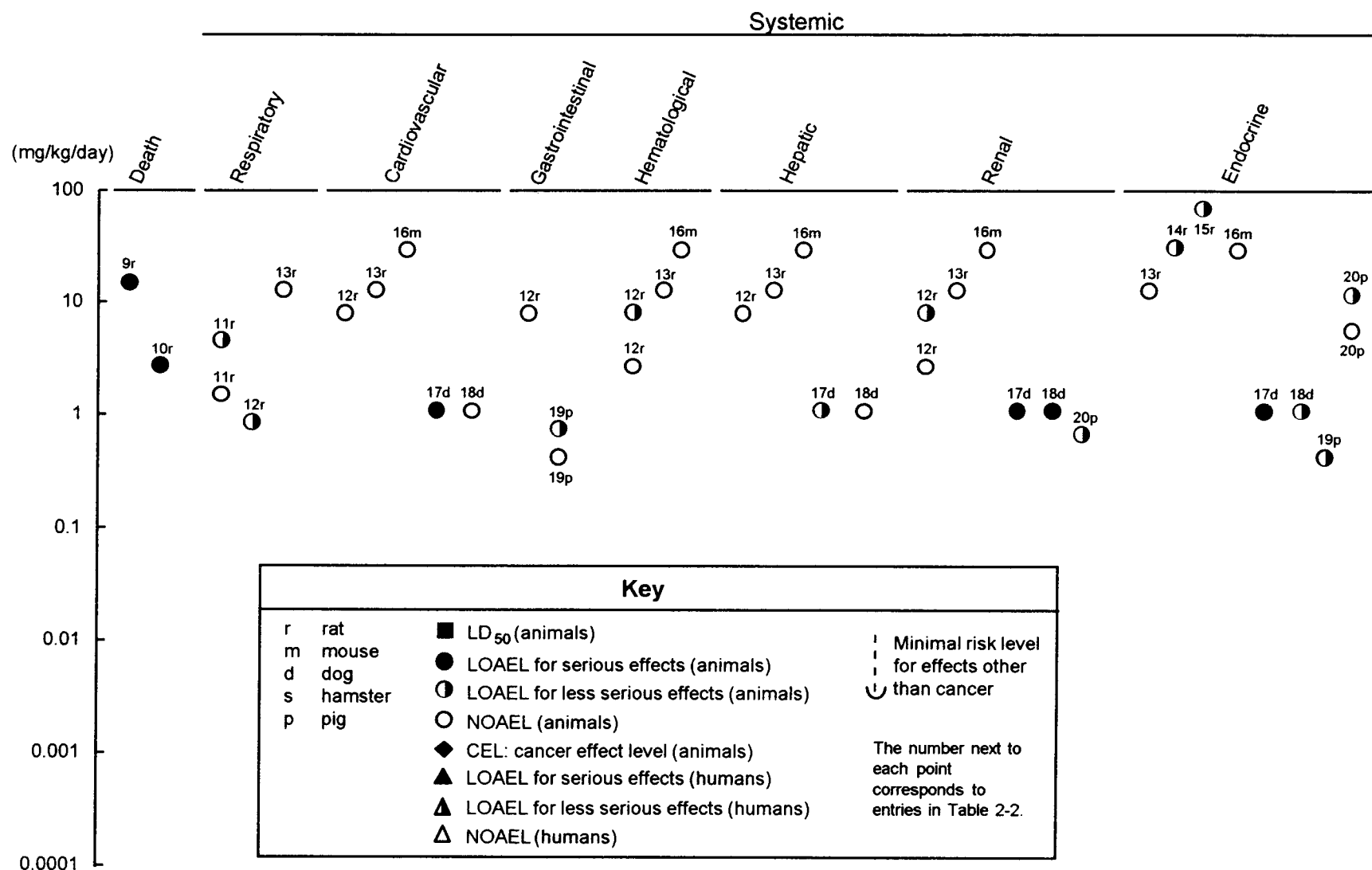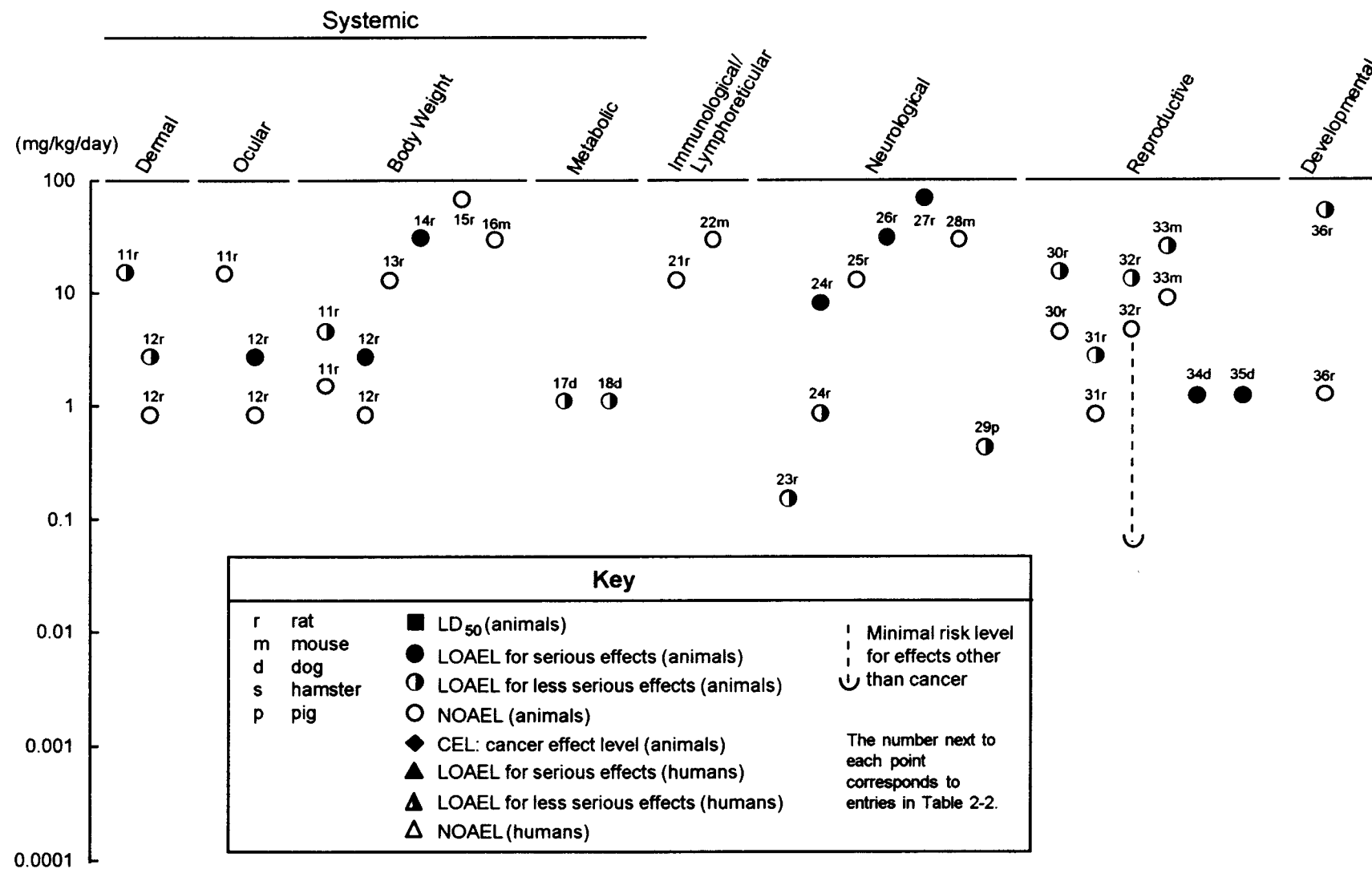## Intermediate (15-364 days)

Figure 2-2. Levels of Significant Exposure to Cyanide - Oral (cont.)

Intermediate (15-364 days)

2. HEALTH EFFECTS

2.2.2.2 Systemic Effects

The systemic effects observed in humans and animals after oral exposure to cyanide are discussed below. The highest NOAEL values and all reliable LOAEL values for each systemic effect in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

Respiratory Effects. Breathing irregularities occur after cyanide poisoning through oral exposure. Stertorous, deep, and rapid breathing was reported in a man who ingested ≈ 15 mg CN$^-$/kg as potassium cyanide in a suicide attempt (Liebowitz and Schwartz 1948). Shortness of breath and dyspnea were observed in 2 reports of suicide attempts; one man ingested 7.6 mg CN$^-$/kg (Goodhart 1994) and the other man ingested 0.57 mg CN$^-$/kg (Saincher et al. 1994), both as potassium cyanide. A man admitted to a hospital after ingesting an unknown amount of sodium cyanide ceased breathing (Grandas et al. 1989). Tachypnea was also reported in children who were poisoned by cyanide after ingesting apricot pits (Lasch and El Shawa 1981).

Respiratory effects were also observed in animals exposed to cyanide. Labored respiration was reported in rats treated with 4.35 mg CN$^-$/kg/day as copper cyanide by gavage for 90 days (Gerhart 1987a). No effects were reported at 1.45 mg CN$^-$/kg/day. Labored respiration occurred in rats exposed at a lower dose of 0.8 mg CN$^-$/kg/day when administered in a form of potassium silver cyanide for 90 days (Gerhart 1987b). Lung congestion and hemorrhage seen at necropsy were attributed to asphyxia rather than to a direct effect of cyanide. In another study, rats were exposed to 0.2-12.5 mg CN$^-$/kg/day as sodium cyanide in the drinking water for 13 weeks. Changes in absolute lung weight were seen, but they were minor and sporadic, and the authors did not consider them to be treatment related (NTP 1993). No respiratory effects were reported in rats exposed to a target dose of 10.4 mg CN$^-$/kg/day as hydrogen cyanide in their feed for 2 years (Howard and Hanzal 1955). The actual dose, however, may have been considerably lower than 10.4 mg/kg/day due to evaporation of hydrogen cyanide from the food.

Cardiovascular Effects. Several case studies reported cardiovascular effects in humans after oral exposure to cyanide. Weak and shallow pulse, and inaudible heart sounds were observed in a comatose man on hospital admission after ingestion of ≈ 15 mg CN$^-$/kg as potassium cyanide (Liebowitz and Schwartz 1948). Following gastric lavage and glucose infusion, the pulse rate and blood pressure became elevated. An enlarged heart was noted. No cardiovascular effects were reported during the recovery. In another study, children poisoned by apricot pits had hypotension upon hospital admission (Lasch and El Shawa 1981).

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After intermediate- or chronic-duration oral exposure to inorganic cyanides, cardiovascular effects in animals, if any, are minimal. No significant histopathological changes were observed in rats exposed to 2.6 or 7.8 mg CN⁻/kg/day as potassium silver cyanide for 90 days (Gerhart 1987b). Changes in absolute heart weight were seen in male and female mice exposed to 0.3-28.8 mg CN⁻/kg/day as sodium cyanide in the drinking water for 13 weeks, but they were minor and sporadic, and the authors did not consider them to be treatment related (NTP 1993). Dogs fed a diet of cassava ingested 1.04 mg CN⁻/kg/day for 14 weeks and exhibited hemorrhage, pyknotic nuclei, and swelling of muscle fibers in the myocardium, while dogs fed rice to which 1.04 mg CN⁻/kg food was added as sodium cyanide did not show any cardiovascular effects (Kamalu 1993). Furthermore, no cardiovascular effects were observed in rats exposed to an estimated dose of 10.4 mg CN⁻/kg/day as hydrogen cyanide in their feed for 2 years (Howard and Hanzal 1955). The actual dose, however, may have differed from 10.4 mg/kg/day due to evaporation of hydrogen cyanide from the food.

Gastrointestinal Effects. Solutions of sodium and potassium cyanide are alkaline and, as such, can cause corrosive responses in the stomach following ingestion. Vomiting was reported in children who ingested a large number of apricot pits (Lasch and El Shawa 1981) and in a man who ingested 7.6 mg CN-/kg in a suicide attempt (Goodhart 1994). Gastrointestinal spasms were reported in a man who accidentally ingested (and inhaled) an unknown amount of potassium cyanide (Thomas and Brooks 1970). Gastric surgery for extensive necrosis had to be performed in a man after he ingested an unknown amount of sodium cyanide (Grandas et al. 1989).

Diarrhea was observed in rats treated orally with 14.5 mg CN⁻/kg/day copper cyanide for 90 days (Gerhart 1987a). No effects were observed at 4.35 mg/kg/day. However, the diarrhea was probably due to the toxicity of copper. No gastrointestinal effects were found in rats exposed to 7.8 mg CN⁻/kg/day as potassium silver cyanide for 90 days (Gerhart 1987b). However, increased vomiting was reported in fasted pigs in a dose as low as 0.7 mg CN⁻/kg/day given as potassium cyanide for 24 weeks by gavage; however, these animals were experimentally compromised as they were starved (Jackson 1988). Chronic intestinal inflammation occurred in dogs exposed to 20.27 mg CN⁻/kg/day for 14.5 months (Hertting et al. 1960).

Hematological Effects. Information regarding hematological effects in humans after oral exposure to cyanide is limited. No adverse hematologic effects were reported in a man who ingested 15 mg CN-/kg as potassium cyanide (Liebowitz and Schwartz 1948).

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In animals, hematological effects were observed in studies with copper cyanide, potassium silver cyanide, and sodium cyanide. Hemolytic anemia was diagnosed in the group of rats treated by gavage for 90 days with 14.5 mg CN^-/kg/day as copper cyanide (Gerhart 1987a). Decreased erythrocytes were reported together with decreased hemoglobin concentrations and decreased hematocrit. The diagnosis of anemia was supported by microscopic findings of pigmentation of the spleen and liver, presence of hemoglobin in the cytoplasm of the renal convoluted tubule epithelium, and by hyperplasia of hematopoietic tissue (spleen and bone marrow). Decreased hemoglobin was observed also at 4.35 mg CN^-/kg/day. Hemolytic anemia is characteristic of copper toxicity; therefore, the hematological effects can be attributed to copper toxicity rather than to cyanide toxicity. Increased mean corpuscular volume, mean corpuscular hemoglobin concentration, and spleen weight indicated hematological effects in rats exposed to 7.8 mg CN^-/kg/day as potassium silver cyanide for 90 days by gavage. No effects were found at 2.6 mg CN^-/kg/day (Gerhart 1987b). The contribution of silver to the hematological effects is not known. In another study, minimal changes were observed in hematology in rats and mice exposed to sodium cyanide in the drinking water for 13 weeks and the authors did not consider them to be treatment related (NTP 1993).

Musculoskeletal Effects. Muscular rigidity was observed in humans after acute cyanide poisoning (Grandas et al. 1989) and rhabdomyolysis, a clinical syndrome characterized by skeletal muscle injury, was observed in a man who ingested 0.57 mg CN^-/kg/day in a suicide attempt (Saincher et al. 1994). No studies were located regarding musculoskeletal effects in animals after oral exposure to cyanide.

Hepatic Effects. Increased serum creatinine and serum creatinine kinase were observed in a man who ingested 0.57 mg CN^-/kg/day in a suicide attempt (Saincher et al. 1994).

In animals, hepatotoxicity was observed after ingestion of copper cyanide. Male rats treated for 90 days by gavage with 14.5 mg CN^-/kg/day as copper cyanide had increased levels of serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) levels, increased bilirubin and alkaline phosphatase, and decreased globulin levels in the blood (Gerhart 1987a). Liver necrosis was observed in the group of female rats treated with 4.35 mg CN^-/kg/day. However, blood chemistry did not reveal any changes. The hepatic effects of copper cyanide are probably due to the toxicity of copper rather than of cyanide.

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Changes in absolute and relative liver weights were reported in rats exposed to 0.2-12.5 mg CN⁻/kg/day and mice exposed to 0.3-28.8 mg CN⁻/kg/day, both as sodium cyanide in the drinking water for 13 weeks, but they were minor and sporadic, and the authors did not consider them to be treatment related (NTP 1993). In another study, periportal vacuolation and congestion were observed in the livers of dogs fed 1.04 mg CN-/kg/day, as cassava, while no hepatic effects were observed in dogs fed rice containing the same concentration of cyanide, as sodium cyanide, for 14 weeks (Kamalu 1993). No hepatic effects were reported in rats exposed by gavage to 7.8 mg CN⁻/kg/day as potassium silver cyanide for 90 days (Gerhart 1987b) or in rats exposed to an estimated dose of 10.4 mg CN⁻/kg/day as hydrogen cyanide in their feed for 2 years (Howard and Hanzal 1955). The actual dose, however, may have differed from 10.4 mg/kg/day due to evaporation of hydrogen cyanide from the food.

Renal Effects. Information regarding renal effects of cyanide in humans is limited to one report. Albuminuria was found in a man during the first 2 days after ingestion of 15 mg CN-/kg as potassium cyanide in a suicide attempt (Liebowitz and Schwartz 1948).

In animals, decreased kidney weight was observed in rats treated with 14.5 mg CN⁻/kg/day as copper cyanide for 90 days (Gerhart 1987a). No changes were reported at 4.35 mg/kg/day exposure. However, copper toxicity was probably responsible for the kidney effects. Increased blood urea nitrogen was found at 7.8 mg CN⁻/kg/day, but not at 2.6 mg CN⁻/kg/day, as potassium silver cyanide (Gerhart 1987b). The contribution of silver to this effect is not known. No significant changes indicating renal effects were found on analysis of blood samples taken at the end of the experiment. Changes in absolute and relative kidney weights were observed in rats and mice exposed to 0.2-12.5 mg CN-/kg/day and mice exposed to 0.3-28.8 mg CN⁻/kg/day, both as sodium cyanide in the drinking water for 13 weeks, but they were minor and sporadic, and the authors did not consider them to be treatment related (NTP 1993).

Histopathologically, a proliferation of glomerular cells in the kidney was observed in pigs exposed to 0.64 mg CN⁻/kg/day in cassava feed for 110 days (Tewe and Maner 1981b). In another study, vacuolation, swelling, and proximal tubule damage with desquamation of the epithelium and casts were observed in kidneys of dogs fed 1.04 mg CN⁻/kg/day as cassava, while increased urinary protein, casts, and some desquamation, but no damage in proximal tubules, were observed in dogs fed rice with the same concentration of cyanide, as sodium cyanide, for 14 weeks (Kamalu 1993). However, no renal effects were observed in rats exposed to an estimated dose of 10.4 mg CN⁻/kg/day as hydrogen cyanide in their feed for 2 years (Howard and Hanzal 1955); in this study, however, the actual dose may have been different due to evaporation of hydrogen cyanide from the food. Cloudy swelling of epithelial cells of

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renal tubules was reported in 3 dogs; each dog was exposed to a different dose of sodium cyanide (ranging from 0.27 to 1.68 mg CN⁻/kg/day) for 14.5 months (Hertting et al. 1960).

Endocrine Effects. Cyanide occurs naturally in several plants, such as cassava, soybeans, spinach, and bamboo shoots, in which it is generated after ingestion from cyanogenic glycosides. Chronic oral exposure to cyanide in humans who eat cassava as a main carbohydrate source of their diet has been associated with thyroid toxicity. The effects are probably caused by thiocyanate, a metabolite of cyanide which reduces iodine uptake by the thyroid. The incidence of endemic goiter correlated with cassava intake in the Congo, where thyroid uptake of radioiodine was decreased in the goitrous area, compared with the controls (Delange and Ermans 1971). In another study, decreased $FT_4$1 and increased $FT_3$1 levels, T_3/T_4 ratio, and TSH were measured in a cohort from a village where an epidemic of spastic paraparesis was found. However, the incidence of endemic goiter was not elevated in this village. Examined individuals also had very high levels of thiocyanate in serum and urine (Cliff et al. 1986).

Thyroid effects were also found in animals exposed to cyanide. Rats fed a diet containing 30 mg CN⁻/kg/day as potassium cyanide for 4 months had a significant decrease in plasma thyroxine levels and thyroxine secretion rates; at 11 months, treated rats showed no significant decreases in thyroxine concentrations, but had significant increases in relative thyroid weight (Philbrick et al. 1979). When pigs were fed a diet containing potassium cyanide and/or cassava roots during pregnancy, an increase in the maternal thyroid weight and thyroid gland hypofunction were observed after ingestion of 11.3 mg CN⁻/kg/day (Tewe and Maner 1981b). No effects on the thyroid gland were found at 5.6 mg CN⁻/kg/day. In another study, no effects on the thyroid gland were noted at 12.5 mg CN⁻/kg/day in rats given sodium cyanide in drinking water for 13 weeks or in mice given 24.3-28.8 mg CN⁻/kg/day (NTP 1993). However, thyroid effects have been reported at low doses in another study. Decreased thyroid function was found in fasted pigs exposed to 0.4 mg CN⁻/kg/day as potassium cyanide for 24 weeks by gavage; however, the animals were experimentally compromised as they were starved (Jackson 1988).

Effects on the adrenal gland, including swelling of the adrenal cortex, hemorrhage, and fibrosis, were observed in dogs fed 1.04 mg CN⁻/kg/day as cassava, as well as in dogs fed rice with the same concentration of cyanide, as sodium cyanide, for 14 weeks (Kamalu 1993).

Dermal Effects. No studies were located regarding dermal effects in humans after oral exposure to cyanide.

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During intermediate-duration exposure, discolored inguinal fur was found in rats exposed for 90 days to 14.5 mg CN$^-$/kg/day by gavage as copper cyanide (Gerhart 1987a) and to 2.6 mg CN$^-$/kg/day as potassium silver cyanide (Gerhart 1987b).

Ocular Effects. Macular degeneration and optic atrophy were reported in humans who ingested cassava containing an unknown concentration of cyanide (van Heijst et al. 1994).

Ocular opacity was noted in rats exposed to 2.6 mg CN$^-$/kg/day as potassium silver cyanide for 90 days (Gerhart 1987b). No pathological findings were observed during ophthalmological examination of rats exposed to 14.5 mg CN$^-$/kg/day as copper cyanide for 90 days (Gerhart 1987a).

Body Weight Effects. No studies were located regarding body weight effects in humans after oral exposure to cyanide.

Decreased body weight gain was cited as one of the effects of exposure to copper cyanide and potassium silver cyanide. The effect was reported in male rats exposed for 90 days to 4.35 mg CN$^-$/kg/day as copper cyanide, but not in those exposed to 1.45 mg CN$^-$/kg/day for 90 days (Gerhart 1987a). Furthermore, decreased weight gain was found in male rats exposed to 2.6 mg CN$^-$/kg/day as potassium silver cyanide for 90 days (Gerhart 1987b). The presence of the copper or silver may have contributed to the observed decreased body weight. Pregnant hamsters fed 1 .O mg CN$^-$/kg/day in cassava for 10 days during gestation had decreased body weight gain (F&es et al. 1986a). No decrease in body weight gain was observed in female rats exposed to 12.5 mg CN$^-$/kg/day or mice of either sex exposed to 0.3-28.8 mg CN$^-$/kg/day in drinking water for 13 weeks. A slight decrease in body weight gain was observed in male rats exposed to 0.5 and 12.5 mg CN$^-$/kg/day (NTP 1993).

MetabolicEffects. Yen et al. (1995) reported metabolic acidosis in 67% of patients acutely poisoned by unknown concentrations of cyanide.

The only study located in animals regarding metabolic effects reported decreased serum albumin and lowered calcium and potassium levels in dogs fed 1.04 mg CN$^-$/kg/day as cassava or sodium cyanide for 14 weeks (Kamalu 1993)

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2.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans after oral exposure to cyanide.

No significant changes in absolute or relative thymus weight were noted in rats and mice exposed to up to 12.5 and 28.8 mg CN⁻/kg/day, respectively, in drinking water for 13 weeks (NTP 1993).

2.2.2.4 Neurological Effects

Neurologic toxicity following cyanide ingestions differs depending on length of exposure. Neurological effects of cyanide poisoning in humans may correlate with the amount ingested; however, the exact doses consumed by the victims are usually not known, Tremors were reported in a patient who accidentally ingested an unknown amount of fluid containing 2.3% silver cyanide and 6.9% sodium cyanide (Chen and Rose 1952). Children who ingested a large number of apricot pits experienced various neurological effects ranging in severity from headaches to coma (Lasch and El Shawa 1981). The severity of effects corresponded with the amount of ingested pits. Comatose patients were admitted to a hospital after ingesting 15 mg CN⁻/kg (Liebowitz and Schwartz 1948), 7.6 mg CN⁻/kg(Goodhart 1994), 114-229 mg CN⁻/kg (Kasamo et al. 1993), and 5.7 mg CN⁻/kg (Valenzuela et al. 1992), all as potassium cyanide.

Four reports were located regarding development of Parkinsonism in patients after cyanide ingestion. A woman in a light coma had positive Babinski's sign on the right with slight right hemiparesis and dysphonia within 2 weeks after acute cyanide poisoning (Carella et al. 1988). Within 5 years, progressive Parkinsonism, dystonia, and apraxia of the right eye opening was present. Atrophy of the cerebellum and distinct ventricular enlargement in cerebral hemispheres were revealed by computed tomography and magnetic resonance image examinations. In another case, a man went into a coma after ingesting an unknown amount of sodium cyanide (Grandas et al. 1989). Later he regained consciousness, but was apathetic with reduced speech and a loss of balance; dystonia and severe Parkinsonism developed during following years. Computed tomography scan revealed bilateral luciencies in the putamen and external globus pallidus. Severe Parkinsonism also developed in two men who ingested ≈ 5.57 mg CN⁻/kg (Utti et al. 1985) and 8.57 mg CN⁻/kg (Rosenberg et al. 1989), respectively, as potassium cyanide in suicide attempts. Lesions were reported in the globus pallidus and putamen in both cases. However, it must be noted that these studies do not demonstrate a true cause and effect relationship between cyanide exposure and Parkinsonism. In addition, other chemicals, such as manganese and carbon monoxide, and therapy with certain drugs may result in Parkinsonism

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The effects of chronic oral exposure of humans to cyanogenic glucosides were studied in regions of Africa with populations that consume a high level of cassava roots (Howlett et al. 1990; Ministry of Health, Mozambique 1984; Monekosso and Wilson 1966; Money 1958; Osuntokun 1968, 1972; Osuntokun et al. 1969; Tylleskar et al. 1994). In some cases, the diet consisted almost exclusively of cassava roots, due to failure of other food crops (Howlett et al. 1990). A variety of neuropathies have been observed in these regions and the findings correlated with increased blood thiocyanate levels, all collectively termed "tropical ataxic neuropathy" (Osuntokun 1973). Symmetrical hyperreflexia of the upper limbs, symmetrical spastic paraparesis of the lower limbs, spastic dysarthria, diminished visual acuity, peripheral neuropathy, cerebellar signs, and deafness were among the clinical findings (Ministry of Health, Mozambique 1984). Decreased plasma vitamin B_{12} levels were also detected in affected individuals (Monekosso and Wilson 1966). Konzo, a distinct upper motor neuron disease characterized by the sudden onset of varying degrees of symmetric, isolated, nonprogressive spastic paraparesis, has occurred in rural areas of Africa and has been associated with high dietary cyanide exposure from the consumption of insufficiently processed bitter cassava (Tylleskar et al. 1994). However, a recent study reported the isolation of scopoletin, a potent hypotensive and spasmolytic agent, from cassava roots (Obidoa and Obasi 1991). This substance, which remains in cassava during processing, rather than cyanide, was suggested to be the etiological agent in the tropical ataxic neuropathy observed among cassava eaters (Obidoa and Obasi 1991). In addition, protein and vitamin deficiencies may subject people in the tropics who eat cassava to increased risks of tropical neuropathies (Makene and Wilson 1972; Osuntokun 1972; Osuntokun et al. 1969).

The central nervous system is also a primary target of orally administered cyanide in animals. Tremors, convulsions, recumbency, and lethargy were observed in rats exposed to 7.8 mg CN⁻/kg/day as potassium silver cyanide for 90 days by gavage (Gerhart 1987b). Since 28 of 40 rats died at this dose level, some of the effects described may represent nonspecific signs that precede death. Hypoactivity was observed in all exposed groups starting at a dose of 0.8 mg CN⁻/kg/day. Similarly, hypoactivity was reported in rats exposed to ≥0.14 mg CN⁻/kg/day as copper cyanide for 90 days by gavage. At 4.35 mg CN-/kg/day, fixed posture occurred, while pronounced lethargy was noted at 14.5 mg CN⁻/kg/day. Decreased brain weight was reported at 14.5 mg CN⁻/kg/day cyanide (Gerhart 1987a). The severity of effects increased as the dose increased in both of these studies and males seemed to be more sensitive to cyanide toxicity than females. However, silver and/or copper toxicity may have contributed to the observed effects in both of these studies.

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Rats fed a diet containing 30 mg CN⁻/kg/day as potassium cyanide and 67 mg CN⁻/kg/day as thiocyanate for 11.5 months had myelin degeneration in the spinal cord (Philbrick et al. 1979). In a behavioral study, exposure to 0.4 mg CN⁻/kg/day as potassium cyanide by gavage for 24 weeks in fasted pigs led to slower reaction time, reduced exploratory behavior, and increased victimization behavior in pigs however, the animals were experimentally compromised as they were starved (Jackson 1988). In contrast, no neurological effects were reported in rats fed an estimated dose of 10.4 mg CN⁻/kg/day as hydrogen cyanide in their feed for 2 years (Howard and Hanzal 1955). The actual dose, however, may have been considerably lower than 10.4 mg/kg/day due to evaporation of hydrogen cyanide from the food. No histopathological changes to the brain were noted in rats and mice exposed to up to 12.5 and 28.8 mg CN⁻/kg/day, as the sodium salt, respectively, in the drinking water for 13 weeks (NTP 1993). Degenerative changes in ganglion cells were reported in 3 dogs that were exposed to 0.27-l .68 mg CN⁻/kg/day as sodium cyanide in capsules for 14.5 months (Hertting et al. 1960).

The highest NOAEL value and all reliable LOAEL values for neurological effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to cyanide.

Increased early embryonic deaths were reported in rats fed a diet containing 80% cassava powder during gestation, but no reproductive effects were found in a group fed with 50% cassava powder (Singh 198 1). Furthermore, no changes were observed in the number of implantations or resorptions in hamsters fed a cassava diet that provided 10.4 mg CN-/kg/day during gestation (Frakes et al. 1986a). Increased gonadal weight was observed in male rats exposed to 14.5 mg CN⁻/kg/day as copper cyanide (Gerhart 1987a) or 2.6 mg CN⁻/kg/day as potassium silver cyanide, for 90 days (Gerhart 1987b). The NOAEL values were 4.35 mg CN⁻/kg/day (Gerhart 1987a) and 0.8 mg CN⁻/kg/day (Gerhart 1987b), respectively. No effects were observed in female rats in either study. A reduction in the spermatogenic cycle, testicular germ cell sloughing and degeneration, and occasional abnormal cells were noted in dogs fed 1.04 mg CN⁻/kg/day as cassava and in dogs fed rice containing the same concentration of cyanide, as sodium cyanide for 14 weeks (Kamalu 1993).

A number of reproductive effects were observed following exposure of rats and mice to sodium cyanide in the drinking water for 13 weeks (NTP 1993). In male rats, reproductive effects including decreased left

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epididymis weight, left cauda epididymis weight, left testis weight, spermatid heads, and spermatid counts were observed at 12.5 mg CN⁻/kg/day. In female rats, significantly more time was spent in proestrus and diestrus stages, and less time was spent in estrus and metestrus stages in the 4.9 and 12.5 mg CN⁻/kg/day groups. In male mice, a significant decrease in the left epididymal and caudal epididymal weights was noted at 24.3 mg CN⁻/kg/day, but no changes in sperm motility or spermatid head density were observed. No changes were noted on the estrus cycle length in female mice. This study was used as the basis for the oral intermediate MRL as described in the footnote to Table 2-2 and in Appendix A.

The highest NOAEL value and all reliable LOAEL values for reproductive effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.6 Developmental Effects

No studies were located regarding developmental effects in humans after oral exposure to cyanide. Developmental abnormalities (microcephaly with open eyes, limb defects, and growth retardation) were observed in 28% of the fetuses of rats exposed to feed containing 80% cassava powder during gestation (Singh 1981). Teratogenic effects (encephalocele and rib abnormalities) were reported in hamsters exposed to a single oral dose of amygdalin during gestation, but these changes were found only at maternally toxic doses (Willhite 1982). Fetotoxicity (reduced fetal weight and ossification) were found in the offspring of hamsters fed a cassava diet providing 1 .O mg CN⁻/kg/day during pregnancy (Frakes et al. 1986a) or to the cyanogenic glucoside linamarin at 120 or 140 mg/kg (Frakes et al. 1985). Blood cyanide increased to a peak of 110 nmol/mL at 3 hours after such a dose of linamarin or to 140 nmol/mL after amygdalin (Frakes et al. 1986b). In contrast, no major developmental effects were observed in rats that were fed a basal cassava diet providing ≈ 1.2 mg CN⁻/kg/day or in rats whose cassava feed was supplemented with potassium cyanide bringing the total dose to 51 mg CN⁻/kg/day, (assuming young growing rats and pregnant rats consume food each day equivalent to 10% of their body weight) (Tewe and Maner 1981a). The rats were exposed to cyanide during gestation days 16-20 and then for 21 days during lactation. When their offspring were exposed to similar diets providing doses of ≈ 1.2 and 51 mg CN⁻/kg/day, decreased growth was observed in the higher dosed weanlings regardless of the exposure *in utero.* When pigs were fed a cassava diet alone or one supplemented with potassium cyanide for 110 gestation days, no effects on number of fetuses or upon fetal weight were observed in the 11.3-mg CN⁻/kg/day cyanide exposed group (Tewe and Maner 1981b).

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The highest NOAEL value and all reliable LOAEL values for developmental effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans after oral exposure to cyanide. A single oral dose of 1-mg CN^-/kg as potassium cyanide did not inhibit testicular deoxyribonucleic acid

(DNA)-synthesis in mice (Friedman and Staub 1976). Other genotoxicity studies are discussed in Section 2.5.

2.2.2.8 Cancer

No studies were located regarding cancer effects in humans or animals after oral exposure to cyanide.

2.2.3 Dermal Exposure

Chronic dermal exposure of humans to cyanide can occur in occupational settings. However, the main route of exposure is considered to be inhalation and, therefore, the occupational exposure studies are discussed in Section 2.2.1.

2.2.3.1 Death

An average LD_{50} value for dermal exposure of 100 mg CN^-/kg as hydrogen cyanide was estimated for humans (Rieders 1971). Blood cyanide greater than 0.2 µg/mL may be associated with acute signs of cyanide poisoning and deaths occur after blood cyanide reaches 1 µg/mL (Snodgrass 1996).

LD_{50} values were calculated for dermal exposure to cyanides in rabbits; 6.7 mg CN^-/kg when applied as hydrogen cyanide, 7.7 mg CN^-/kg as sodium cyanide, and 8.9 mg CN^-/kg as potassium cyanide (Ballantyne 1983a). Moistening the skin slightly lowered, and abrading the skin substantially lowered, the dermal LD_{50} of cyanide as sodium cyanide (Ballantyne 1988). Similar differences in toxicity of various chemical forms of cyanide were observed after cyanide was applied to the inferior conjunctival sac of one eye (Ballantyne 1983a, 1983b, 1988). Transocular LD_{50}, values were 1.0 mg CN^-/kg as hydrogen cyanide, 2.68 mg CN^-/kg as sodium cyanide, and 3.2 mg CN^-/kg as potassium cyanide. The deaths occurred within

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3-12 minutes. Deaths occurred also in guinea pigs when their skin was exposed to hydrogen cyanide, however, the doses could not be quantified (Fairley et al. 1934; Walton and Witherspoon 1926). The LD,, values for death are recorded in Table 2-3.

2.2.3.2 Systemic Effects

No studies were located regarding hematological, musculoskeletal or hepatic effects in humans or animals after dermal exposure to cyanide. The systemic effects observed in humans and animals after dermal exposure to cyanide are discussed below. The highest NOAEL values and all reliable LOAEL values for each systemic effect in each species and duration category are recorded in Table 2-3.

Respiratory Effects. Breathing irregularities including Cheyne-Stokes respiration developed in two persons who fell into cisterns containing copper cyanide or potassium cyanide (Dodds and McKnight 1985; Trapp 1970) or whose hands were exposed to hydrogen cyanide (Potter 1950). The effects reflect the central nervous system toxicity of cyanide.

Rapid breathing was reported as the first sign of toxicity in rabbits that received 0.9 mg CN'/kg as hydrogen cyanide, 1.69 and 2.1 mg CN⁻/kg as sodium cyanide, and 2.5 mg CN⁻/kg as potassium cyanide in their conjunctival sacs (Ballantyne 1983b, 1988). Similarly, labored or rapid breathing preceded coma and death in guinea pigs exposed dermally to unknown doses of hydrogen cyanide (Fairley et al. 1934; Walton and Witherspoon 1926).

Cardiovascular Effects. Peripheral vasoconstriction and gross plasma extravasation were reported in a man who accidentally fell into a cistern with hot copper cyanide (Dodds and McKnight 1985). Palpitations were recorded in 3 men who wore respiratory masks while working in an atmosphere containing 20,000 ppm hydrogen cyanide for 8-10 minutes (Drinker 1932). The masks were reported to give excellent respiratory protection. Therefore, the effects seen in these men may have been due to dermal exposure.

No studies were located regarding cardiovascular effects in animals after dermal exposure to cyanide.

Table 2-3. Levels of Significant Exposure to Cyanide - Dermal

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL	LOAEL		Reference Chemical Form
				Less Serious	Serious	
ACUTE EXPOSURE						
Death						
Rabbit (NS)	once				8.9 mg/kg F (dermal LD$_{50}$)	Ballantyne 1983a KCN
Rabbit (NS)	once				6.7 mg/kg F (dermal LD$_{50}$)	Ballantyne 1983a HCN
Rabbit (NS)	once				7.7 mg/kg F (dermal LD$_{50}$)	Ballantyne 1983a NaCN
Rabbit (albino)	once				3.2 mg/kg F (transocular LD$_{50}$)	Ballantyne 1983a, 1983b KCN
Rabbit (albino)	once				1.0 F (transocular LD$_{50}$) mg/kg	Ballantyne 1983a, 1983b HCN
Rabbit (New Zealand)	once				4.1 F (dermal LD$_{50}$ -abraded skin) mg/kg	Ballantyne 1988 NaCN
Rabbit (New Zealand)	once				6.3 F (dermal LD$_{50}$-moist skin) mg/kg	Ballantyne 1988 NaCN
Rabbit (New Zealand)	once				2.4 F (transocular LD$_{50}$) mg/kg	Ballantyne 1988 NaCN
Systemic						
Human	8-10 min	Cardio		20000 M (palpitations) ppm		Drinker 1932 HCN

Table 2-3. Levels of Significant Exposure to Cyanide - Dermal (continued)

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL	LOAEL		Reference Chemical Form
				Less Serious	Serious	
Rabbit (albino)	once	Resp		2.5 F (rapid breathing) mg/kg		Ballantyne 1983b KCN
		Ocular			2.5 mg/kg F (corneal opacity, keratitis)	
Rabbit (albino)	once	Resp		0.9 F (rapid breathing) mg/kg		Ballantyne 1983b HCN
		Ocular			0.9 mg/kg F (corneal opacity, keratitis)	
Rabbit (albino)	once	Resp	1.69 F mg/kg	2.1 F (rapid breathing) mg/kg		Ballantyne 1983b NaCN
		Ocular	1.69 F mg/kg		2.1 F (corneal opacity, keratitis) mg/kg	
Neurological						
Human	8-10 min			20,000 M (dizziness, weakness, ppm headache)		Drinker 1932 HCN
Rabbit (albino)	once				0.9 mg/kg F (convulsions and loss of consciousness)	Ballantyne 1983b HCN
Rabbit (New Zealand)	once				2.5 F (convulsions and loss of mg/kg consciousness)	Ballantyne 1983b KCN
Rabbit (albino)	once		1.7 F mg/kg		2.1 F (convulsions and loss of mg/kg consciousness)	Ballantyne 1983b NaCN

Cardio = cardiovascular; d = day(s); F = female; HCN = hydrogen cyanide; KCN = potassium cyanide; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed- adverse-effect level; M = male; min = minutes; NaCN = sodium cyanide; NOAEL = no-observed-adverse-effect level; NS = not specified; Resp = respiratory

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Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans after dermal exposure to cyanide.

Acute dermal exposure of guinea pigs to an unknown concentration of hydrogen cyanide resulted in submucous hemorrhages in the stomach as observed at necropsy (Fairley et al. 1934).

Renal Effects. The information regarding renal effects following dermal exposure to cyanide in humans is limited to one case report. Transitory oliguria (scanty urination) was observed in a patient who accidentally fell into a cistern containing 1,000 gallons of hot copper cyanide and remained there for 3 minutes before being rescued (Dodds and McKnight 1985).

No studies were located regarding renal effects in animals after dermal exposure to cyanide.

Dermal Effects. No studies were located regarding dermal effects in humans after dermal exposure to cyanide.

When the skin of rabbits was exposed to 5,000 ppm cyanide as cyanogen for 8 hours, no dermal lesions were found (McNerney and Schrenk 1960). Vascular congestion was reported in the skin of guinea pigs after exposure to unknown doses of hydrogen cyanide for 65 minutes (Fairley et al. 1934).

Ocular Effects. No studies were located regarding ocular effects in humans after dermal exposure to cyanide.

Cyanide toxicity was tested in rabbits by applying 1.69-5.28 mg CN^-/kg/day as sodium cyanide to the inferior conjunctival sac of one eye (Ballantyne 1983b, 1988). Irritation, lacrimation, and conjunctival hyperemia were present immediately after the treatment. Keratitis developed in some rabbits after a cyanide application of 0.9 mg CN^-/kg as hydrogen cyanide, 2.1 mg CN^-/kg as sodium cyanide, and 2.5 mg CN^-/kg as potassium cyanide.

2.2.3.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans or animals after dermal exposure to cyanide.

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2.2.3.4 Neurological Effects

Deep coma developed in two persons who accidentally fell into cisterns containing copper cyanide (Dodds and McKnight 1985) and potassium cyanide, respectively (Trapp 1970). Similarly, a worker, whose hand was exposed to liquid hydrogen cyanide, fell into a coma, lost deep reflexes, and showed dilated pupils within 5 minutes (Potter 1950). Men working in an atmosphere containing 20,000 ppm hydrogen cyanide for 8-10 minutes experienced dizziness, weakness, and headaches (Drinker 1932). The workers wore masks that were reported to give excellent respiratory protection. However, exposure to such high concentrations is not safe because the gas is absorbed through the unprotected skin. The effects seen in these men may have been due to dermal exposure.

Weak and ataxic movements, convulsions, and coma developed in rabbits that received 0.9 mg CN^-/kg as hydrogen cyanide, 2.1 mg CN^-/kg as sodium cyanide, and 2.5 mg CN^-/kg as potassium cyanide into their conjunctival sacs (Ballantyne 1983b, 1988). Rabbits exposed dermally to 1.92 mg CN^-/kg as hydrogen cyanide, 4.0 mg CN^-/kg as potassium cyanide or 2.6 mg CN^-/kg as sodium cyanide exhibited tremors, retrocolic spasms, and convulsions (Ballantyne 1994). Similarly, convulsions and coma preceded death in guinea pigs exposed dermally to unknown doses of hydrogen cyanide (Fairley et al. 1934; Walton and Witherspoon 1926).

All reliable LOAEL values for neurological effects in each species for acute duration are recorded in Table 2-3.

No studies were located regarding the following health effects in humans or animals after dermal exposure to cyanide:

2.2.3.5 Reproductive Effects

2.2.3.6 Developmental Effects

2.2.3.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.5.

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2.2.3.8 Cancer

No studies were located regarding cancer in humans or animals after dermal exposure to cyanide.

2. 3 TOXICOKINETICS

Cyanide gas and certain salts are rapidly absorbed following inhalation, oral, and dermal exposure. Following inhalation, it is rapidly distributed throughout the body, with measurable levels detected in all organs studied to date. Cyanide can be distributed in the body within seconds and death can occur within minutes. Following oral exposure, the highest levels have been detected in the lungs and blood. Animal studies have shown that cyanide does not accumulate in the blood and tissues following chronic oral exposure. Cyanide is transformed to thiocyanate in the body, with a plasma half-life of 20 minutes to one hour. Cyanide metabolites are excreted primarily in the urine, with small amounts excreted through the lungs.

2.3.1 Absorption

2.3.1.l Inhalation Exposure

Cyanide is rapidly absorbed (within seconds) following inhalation exposure. Humans retained 58% of hydrogen cyanide in the lungs after inhaling the gas through normal breathing (Landahl and Herrmann 1950).

Quantitative data on the absorption of hydrogen cyanide by inhalation were reported in dogs (Gettler and Baine 1938). During exposure to an unknown concentration of hydrogen cyanide, one dog reportedly absorbed 16.0 mg (1.55 mg/kg); the other dog absorbed 10.1 mg (1.11 mg/kg). These doses were fatal to the dogs in 15 and 10 minutes, respectively. More recent quantitative data were not available.

2.3.1.2 Oral Exposure

Information regarding the rapid lethal effects following oral intake of cyanide in humans indicates that cyanide is rapidly absorbed from the gastrointestinal tract. In a case study, an 80-kg male ingested an estimated 15-25 mg CN⁻/kg as potassium cyanide in a suicide attempt (Liebowitz and Schwartz 1948). Based on a concentration of 200 mg hydrogen cyanide/L in the blood 2 hours after ingestion, it was

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estimated that the patient had 1.2 g hydrogen cyanide in the blood, with -2.3 g CN⁻ in the body, after
2 hours.

Three dogs were given lethal doses of cyanide by gavage. The amount of cyanide absorbed was
determined by the difference between the cyanide given and the cyanide left in the stomach and intestines
(Gettler and Baine 1938). The dogs died 8,21, and 155 minutes after treatment and had absorbed 17,24,
and 72%, respectively, of the dose given. Rats excreted 47% of a dose of radioactivity in the urine during
24 hours following gavage treatment with 2 mg CN⁻/kg as radiolabeled potassium cyanide (Farooqui and
Ahmed 1982), indicating that at least 53% of the cyanide was absorbed in 24 hours. More detail on the
mechanism of absorption is provided in Section 2.4.1.

2.3.1.3 Dermal Exposure

No studies were located regarding quantitative absorption in humans after dermal exposure to cyanide gas
or common inorganic salts. Evidence that cyanide can be absorbed through the skin of humans is
provided in case reports of toxic effects in humans after accidental dermal contact with cyanide (see
Section 2.2.3).

Information regarding dermal absorption of cyanide in animals was provided in studies of guinea pigs and
dogs (Walton and Witherspoon 1926). When a small area of the shaved abdomen of guinea pigs was
exposed to hydrogen cyanide vapor for 30-60 minutes, signs of cyanide toxicity observed included rapid
respiration followed by general twitching of muscles, convulsions, and death. In a similar experiment,
shaved and unshaved dogs were placed in a chamber in which their bodies, with the exception of the head
and neck, were exposed to hydrogen cyanide vapor. No signs of toxicity were reported after exposure to
4,975 ppm hydrogen cyanide for 180 minutes. Deaths occurred after exposure to 13,400 ppm hydrogen
cyanide for 47 minutes and suggested dermal absorption. Further indirect evidence regarding dermal
absorption of cyanide as hydrogen cyanide or its salts (Ballantyne 1983a, 1983b, 1988) can be found in
Section 2.2.3.

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2.3.2 Distribution

2.3.2.1 Inhalation Exposure

Once cyanide is absorbed, it is rapidly distributed by the blood throughout the body. Tissue levels of hydrogen cyanide were 0.75, 0.42, 0.41,0.33, and 0.32 mg/100 g of tissue in the lung, heart, blood, kidney, and brain, respectively, in a man who died following inhalation exposure to hydrogen cyanide gas. In one case of death due to cyanide exposure, it was estimated that 30 mg of hydrogen cyanide had been ingested and that 3 hours had elapsed before death (Gettler and Baine 1938). In another case, tissue cyanide levels from a man who died from inhalation of hydrogen cyanide were reported as 0.5 mg per 100 mL of blood and 0.11,0.07, and 0.03 mg/l00 g in the kidney, brain, and liver, respectively. Urinary cyanide levels were reported as 0.2 mg/l00 mL, and 0.03 mg/l00 g were found in the gastric contents (Finck 1969). Following chronic occupational exposure to 0.19-0.75 ppm hydrogen cyanide, 56.0 and 18.3 yg CN-/100 mL were found in the blood of smokers and nonsmokers, respectively (Chandra et al. 1980). The cyanide levels in control groups were 4.8 yg/mL for smokers and 3.2 μg/mL for nonsmokers. In two dogs exposed to unspecified fatal concentrations of hydrogen cyanide, the highest cyanide levels were found in the lungs, blood, and heart (Gettler and Baine 1938). Rats exposed to hydrogen cyanide gas at 356 or 1,180 ppm died within 10 and 5 minutes, respectively (Yamamoto et al. 1982). Samples taken immediately after respiration stopped, showed that the pattern of tissue distribution of cyanide did not vary with the concentration used. In averaging data for both dose groups, tissue concentrations, reported as l.tg/g wet weight (ww), were 4.4 in the lungs, 3.0 in the blood, 2.15 in the liver, 1.4 in the brain, and 0.68 in the spleen. Thus, the highest cyanide concentrations were observed in the lung. Rabbits exposed to hydrogen cyanide at 2,714 ppm for 5 minutes had blood and serum cyanide levels of 170 and 48 μg/dL, and tissue levels (in units of μg/l00 g) of 0 in the liver, 6 in the kidney, 50 in the brain, 62 in the heart, 54 in the lung, and 6 in the spleen (Ballantyne 1983a).

2.3.2.2 Oral Exposure

Small but significant levels of cyanide are present in normal blood plasma at concentrations of 0-14 μg %. (Feldstein and Klendshoj 1954). Vitamin B_{12} contains cyanide, with the source of cyanide attributed to breakdown of cyanogenic foods by bacteria in the gut.

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Cyanide levels in a woman who died 30 minutes after ingesting ≈ 1,325 mg cyanide as sodium cyanide were, in mg %: stomach contents, 3.2; brain, 0.7; urine, 0.5; blood, 0.4; kidney, 0.2; stomach wall, 0.2; and liver, 0.1 (Ansell and Lewis 1970). The mean organ levels of cyanide ion in cases of fatal poisoning in 17-58 cases were, in mg %: stomach contents, 160; spleen, 3.77; blood, 2.39; liver, 1.62; brain, 1.2; kidney, 0.61; and urine, 0.06 (Ansell and Lewis 1970). Brain cyanide levels ranged from 0.06 to 1.37 mg hydrogen cyanide/100 g of tissue in 4 humans who ingested fatal doses of cyanide (Gettler and Baine 1938). Cyanide levels in the livers of 6 humans ranged from 0.22 to 0.91 mg hydrogen cyanide1100 g of tissue. In two cases in which men died from ingestion of unknown quantities of unspecified cyanide salts, cyanide levels were highest in the gastric contents, and next highest in the lungs and blood (Finck 1969).

Combined data from 9 to 10 rats that died 3.3 and 10.3 minutes after gavage doses of 7 or 21 mg CN-/kg as sodium cyanide showed average tissue concentrations of cyanide in l μg/g ww of: liver, 8.9; lung, 5.8; blood, 4.9; spleen, 2.1; and brain, 1.5 (Yamamoto et al. 1982). When 6 rats were treated with 4 mg CN$^-$/kg as potassium cyanide, signs of central nervous system toxicity were observed (Ahmed and Farooqui 1982), and cyanide levels 1 hour after exposure were 3,380 μg /g in liver, 748 μg /g in brain, and 550 μg/g in kidney. In a study using orally administered radioactively labelled potassium cyanide, the radioactivity detected in whole blood or plasma decreased rapidly within 6 hours. Of the low levels of radioactivity detected in red blood cells, about 94% of the radioactivity recovered was found in the hemolysate; of which 70% was detected in the heme fraction; 14-25% in globin; and only 5-10% in cell membranes (Farooqui and Ahmed 1982). Rabbits treated by gavage with 11.9-20.3 mg CN$^-$/kg as hydrogen cyanide had blood and serum cyanide levels of 480 and 252 pg/dL respectively, and tissue levels (μg/100 g wet tissue) of 512 in liver, 83 in kidney, 95 in brain, 105 in the heart, 107 in the lung, and 72 in the spleen at the time of death (Ballantyne 1983a).

Cyanide has not been shown to accumulate in the blood and tissues following chronic oral exposure to inorganic cyanides. Following the treatment of groups of 10 male and 10 female rats with hydrogen cyanide in the diet at < 10.4 mg CN$^-$/kg/day for 2 years, virtually no cyanide was found in plasma or kidneys (Howard and Hanzal 1955). Low levels were found in erythrocytes (mean of 1.9 μg /l00 g). Levels of thiocyanate, the less toxic primary metabolite of cyanide, increased 3.5-fold in plasma, 3.3-fold in erythrocytes, 1.3-fold in liver, and 2.5-fold in kidney.

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2.3.2.3 Dermal Exposure

No studies were located regarding distribution in humans after dermal exposure to cyanide.

Six rabbits exposed dermally to 33.75 mg CN⁻/kg as hydrogen cyanide had blood and serum cyanide levels of 310 and 144 pg/dL, respectively, and tissue levels µg /100 g) of 26 in liver, 66 in kidney, 97 in brain, 110 in heart, 120 in lungs, and 21 in the spleen (Ballantyne 1983a). Cyanide concentrations were measured immediately after rabbits died, 3-12 minutes after administration of 5.25 mg CN⁻/kg as hydrogen cyanide, sodium cyanide, or potassium cyanide to their conjunctival sac (Ballantyne 1983b). Higher cyanide levels were observed in whole blood than in serum in all three groups. However, blood and serum cyanide levels were significantly lower in sodium cyanide and potassium cyanide groups than in the hydrogen cyanide group. Hydrogen cyanide-treated rabbits also had higher concentrations of cyanide in myocardium, lungs, and brain than rabbits from the other two groups. In all groups, the least amount of cyanide was found in the liver and kidney.

2.3.3 Metabolism

Reports of ingestion of cyanides by humans and reports of occupational exposure (see Section 2.5.1) indicate that cyanide is transformed into thiocyanate. A plasma half-life of 20 minutes to 1 hour has been estimated for cyanides in humans after nonlethal exposures (Hartung 1982).

The metabolism of cyanide has been studied in animals. The proposed metabolic pathways shown in Figure 2-3 are (1) the major pathway, conversion to thiocyanate by either rhodanese or 3-mercaptopyruvate sulfur transferase; (2) conversion to 2-aminothiazoline-4-carboxylic acid (Wood and Cooley 1956); (3) incorporation into a 1 -carbon metabolic pool (Boxer and Richards 1952); or (4) combining with hydroxocobalamin to form cyanocobalamin (vitamin B_{12}) (Ansell and Lewis 1970). Thiocyanate has been shown to account for 60-80% of an administered cyanide dose (Blakley and Coop 1949; Wood and Cooley 1956) while 2-aminothiazoline-4-carboxylic acid accounts for about 15% of the dose (Wood and Cooley 1956). The conversion of cyanide to thiocyanate was first demonstrated in 1894. Conversion of cyanide to thiocyanate is enhanced when cyanide poisoning is treated by intravenous administration of a sulfur donor (Smith 1996; Way 1984). The sulfur donor must have a sulfane sulfur, a sulfur bonded to another sulfur (e.g., sodium thiosulfate). During conversion by rhodanese, a sulfur atom is transferred from the donor to the enzyme, forming a persulfide intermediate. The persulfide sulfur is then transferred

Figure 2-3. Basic Processes Involved in the Metabolism of Cyanide
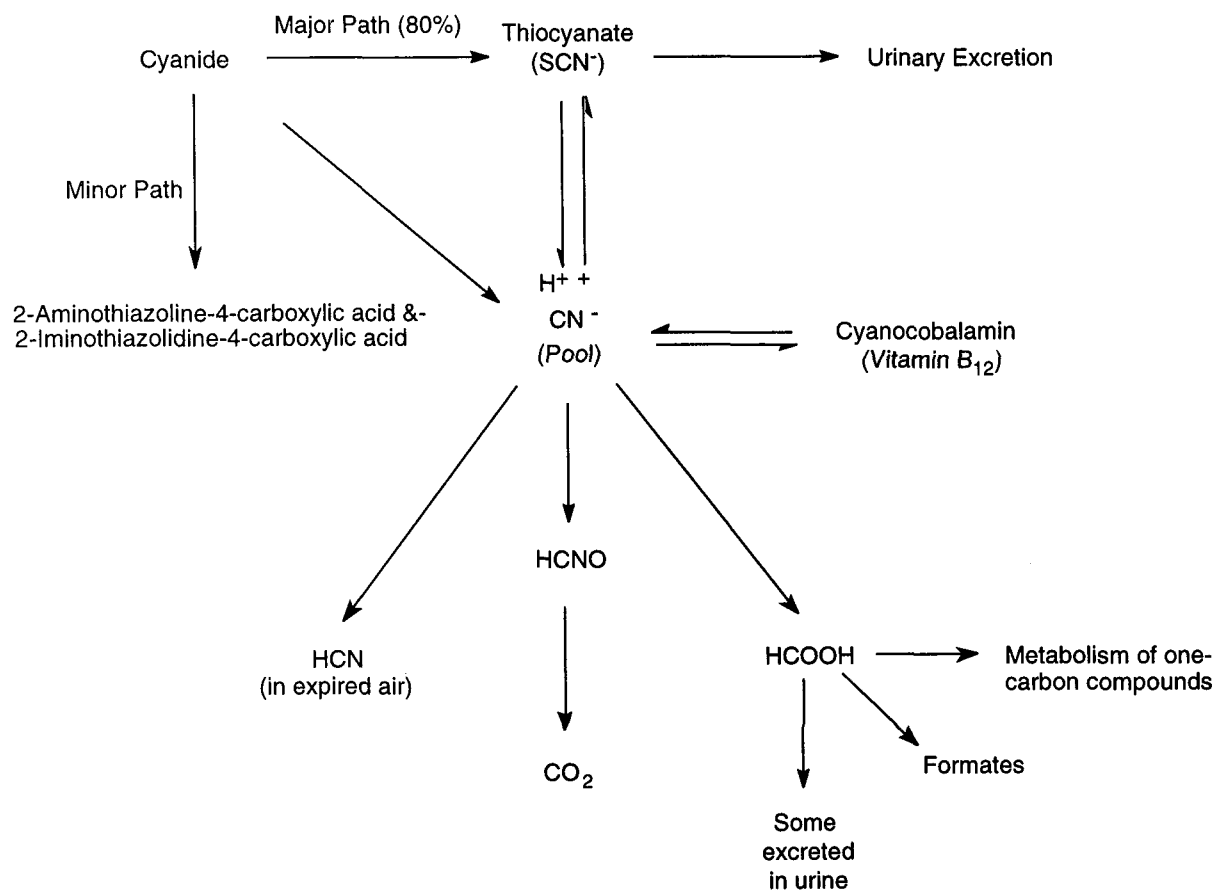
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from the enzyme to cyanide, yielding thiocyanate. Thiocyanate is then readily excreted in the urine as the major metabolite. Once thiocyanate is formed, it is not converted back to cyanide.

Radioisotopic studies showed that albumin interacts with the sulfane pool and that the serum albuminsulfane sulfur carrier complex can react with cyanide (Schneider and Westley 1969). Higher hepatic rhodanese and lower serum albumin levels were found in mice fed a protein-free diet for 14 days compared with mice fed a control diet (Rutkowski et al. 1985). Despite the higher rhodanese levels, mortality following an intraperitoneal injection of sodium cyanide was higher in mice fed the protein-free diet both with and without thiosulfate pretreatment. In mice fed the control diet in reduced amounts, serum albumin levels were higher than controls. Mortality in food-deprived mice was also higher compared with controls, but only at high cyanide doses when thiosulfate was also administered. However, the pharmacokinetic studies in dogs suggest that the sulfane sulfur pool may play an important role as the central compartment for cyanide detoxification (Sylvester et al. 1983; Way 1984).

The species and tissue distribution of rhodanese is highly variable (Himwich and Saunders 1948). In dogs, the highest activity of rhodanese was found in the adrenal gland, ≈ 2.5 times greater than the activity in the liver. Monkeys, rabbits, and rats had the highest rhodanese activity in the liver and kidney, with relatively low levels in the adrenals. It should be noted that total rhodanese activity in other species was higher than in dogs, which is consistent with the greater susceptibility of dogs to the acute effects of cyanide. Similar low levels of activity of the enzyme were found for the brain, testes, lungs, spleen, and muscle among various species.

In vitro studies with rat tissues indicated that rhodanese activity was ≈ 7 times higher in the nasal mucosa than in the liver (Dahl 1989). Furthermore, kinetic constants for rhodanese in mitochondria were higher in nasal than in liver tissue.

Figure 2-4 illustrates the minor pathway for metabolism of cyanide in mammalian systems in which cyanide chemically combines with the amino acid cystine. This chemical reaction yields cysteine and β-thiocyanoalanine that is further converted to form 2-aminothiazoline-4-carboxylic acid and its tautomer, 2-iminothiazolidiene-4-carboxylic acid.

Reactions of cyanide with the salts or esters of some amino acids (e.g., pyruvate, α-ketoglutarate, oxaloacetate) lead to formation of cyanohydrin intermediates and their incorporation into intermediary metabolism.

Figure 2-4. Minor Path for the Removal of Cyanide from the Body

Cystine

β-Thiocyanoalanine

2-Aminothiazoline-4-carboxylic acid

2-Imino-4-thiazolidine-carboxylic acid
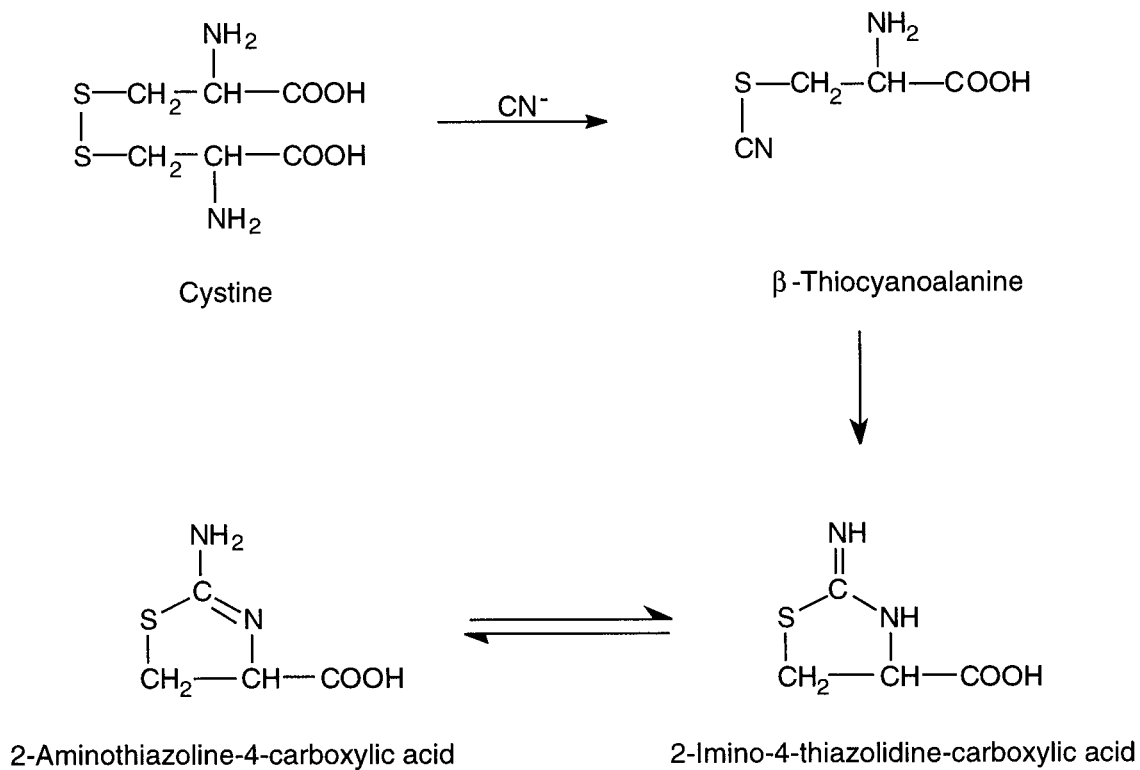
Source: Ansell and Lewis 1970

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The ability of cyanide to form complexes with some metallic ions such as cobalt is the basis for the reaction with hydroxocobalamin that yields cyanocobalamin. Cyanocobalamin (vitamin B $_{12}$), which contains cyanide and cobalt, is essential for the health of mammalian organisms.

2.3.4 Elimination and Excretion

2.3.4.1 Inhalation Exposure

Following chronic occupational exposure to 0.19-0.75 ppm hydrogen cyanide, 24-hour urinary levels of thiocyanate were 6.23 (smokers) and 5.4 µg /mL (nonsmokers) in exposed workers as compared with 3.2 (smokers) and 2.15 µg /mL (nonsmokers) in the controls (Chandra et al. 1980). This study demonstrates that tobacco smoking contributes to higher thiocyanate levels excreted in the urine. No studies were located regarding excretion of cyanide in animals after inhalation exposure to cyanide.

2.3.4.2 Oral Exposure

Cyanide metabolites are normally excreted in urine (Vassel et al. 1944) with small amounts eliminated through the lungs. Urinary excretion of thiocyanate was monitored in a man after ingestion of $\approx$ 3-5 g potassium cyanide (15-25 mg CN^-/kg) (Liebowitz and Schwartz 1948). The results indicated that the patient excreted 237 mg of thiocyanate over a 72-hour period. This quantity was substantially more than the normal average amount of thiocyanate in urine, which varies between 0.85 and 14 mg/24 hours. Thirty-one children who had consumed flour made from insufficiently processed cassava had mean urinary thiocyanate levels of 757 ymol/L, compared with 50 µmol/L in those children who had consumed sufficiently processed cassava (Tylleskar et al. 1992). In another study (Mlingi et al. 1993), mean urinary thiocyanate was 490 µmol/L in a village affected by Konzo disease, and 350 µmol/L in an unaffected village, with the villages being comparable in all other respects.

When rats were given 2 mg CN^-/kg [^{12}C] potassium cyanide, urinary excretion of radioactivity reached 47% of the dose within 24 hours following administration (Farooqui and Ahmed 1982). When [^{14}C] sodium cyanide was injected subcutaneously into rats at a level of 8.3 µmol, no difference in radioactivity eliminated was observed between the group pretreated for 6 weeks with a diet containing 0.7 mg CN^-/kg as potassium cyanide and their matching controls (Okoh 1983). Most of the radioactivity was detected in the urine (89% by 24 hours). Thiocyanate was the major metabolite. About 4% of the radioactivity was expired, mostly as carbon dioxide.

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2.3.4.3 Dermal Exposure

No studies were located regarding excretion in humans or animals after dermal exposure to cyanide.

2.3.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen et al. 1987; Andersen and Krishnan 1994). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parametrization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 199Os, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substancespecific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

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The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) is adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically-sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 2-5 shows a conceptualized representation of a PBPK model.

If PBPK models for cyanide exist, the overall results and individual models are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations.

No PBPK models were located for cyanide.

2.4 MECHANISMS OF ACTION

This section presents a brief overview of any known mechanisms of metabolism, absorption, distribution, and excretion including substance reactions or physiological processes that lead to or comprise the mechanism(s) of toxic effect.

2.4.1 Pharmacokinetic Mechanisms

Absorption. Absorption of cyanide across the gastrointestinal mucosa depends on the pH of the gut and the pKa and lipid solubility of the particular cyanide compound. Hydrogen cyanide is a weak acid with a pKa of 9.2 at 25 °C. The acidic environment in the stomach favors the non-ionized form of hydrogen cyanide and facilitates absorption. Information regarding the rapid lethal effects following oral intake of cyanide in humans (Gosselin et al. 1976) indicates that cyanide is rapidly absorbed from the gastrointestinal tract.

Figure 2-5. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance

Inhaled chemical — — — ┐   ┌ — — →Exhaled chemical

Ingestion

Lungs

Liver

V_{max} K_m

GI Tract

VENOUS BLOOD

ARTERIAL BLOOD

Fat

Slowly perfused tissues

Richly perfused tissues

Kidney

Urine

Skin

Chemicals in air contacting skin
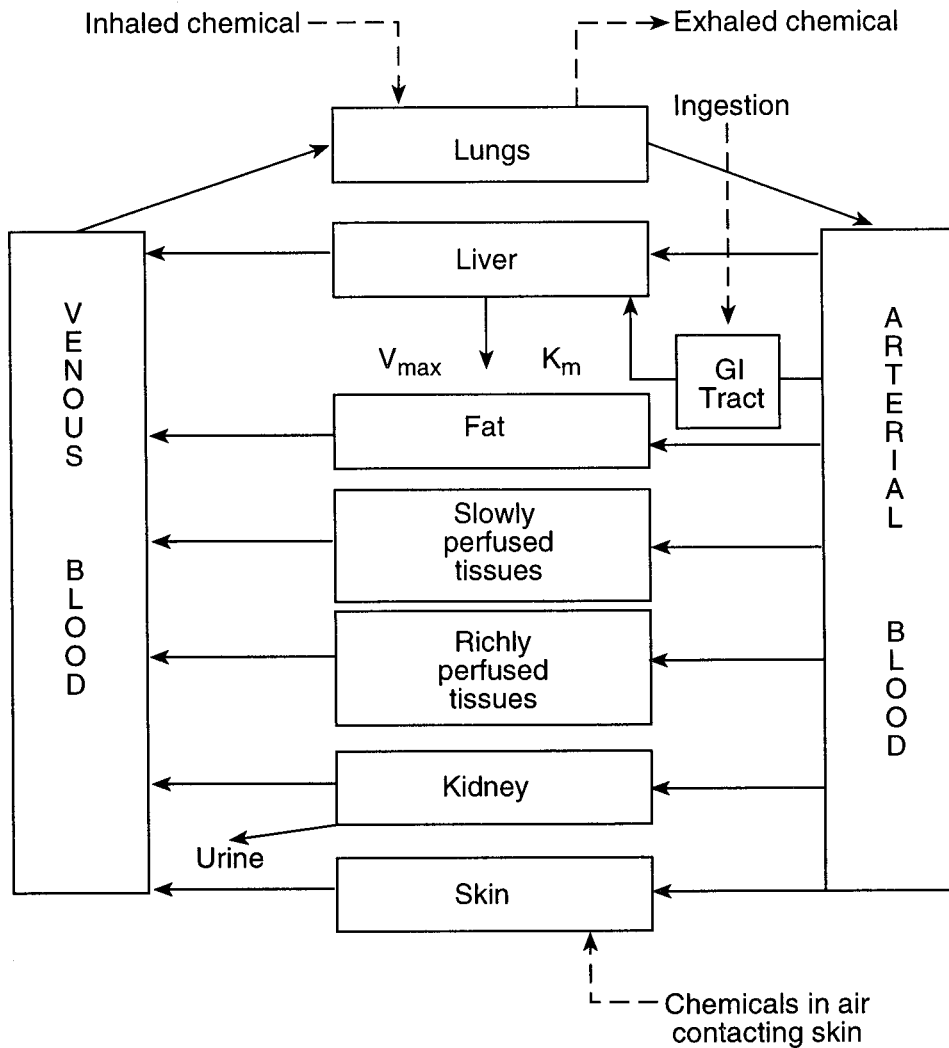
Source: adapted from Krishnan et al. 1992

Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

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Hydrogen cyanide is moderately lipid-soluble, which, along with its small size, allows it to rapidly cross mucous membranes, to be taken up instantly after inhalation, and to penetrate the epidermis. In addition, some cyanide compounds, such as potassium cyanide, have a corrosive effect on the skin that can increase the rate of percutaneous absorption (NIOSH 1976). Information regarding dermal absorption in animals and evidence that cyanide can be absorbed through the skin of humans is provided in Sections 2.3.1.3 and 2.2.3, respectively.

Distribution. Cyanide is rapidly distributed by the blood throughout the body. In a study using orally administered radioactively labelled potassium cyanide, radioactivity detected in whole blood or plasma decreased rapidly within 6 hours. Of the low levels of radioactivity detected in the red blood cells, about 94% of the radioactivity recovered was found in the hemolysate; of which 70% was detected in the heme fraction, 14-25% in globin, and only 5-10% in cell membranes (Farooqui and Ahmed 1982). Yamamoto et al. (1982) determined that the pattern of distribution of cyanide did not vary with the concentration used. Ballantyne (1983b) observed higher cyanide levels in whole blood than in serum in rabbits exposed dermally to hydrogen cyanide, potassium cyanide, and sodium cyanide. See Section 2.3.2.1 for specific studies on cyanide tissue distribution.

Cyanide is a reactive chemical substance and has the potential to form a variety of adducts in biological systems. A study of radiolabeled cyanide binding to mouse brain parts revealed that the hypothalamus accumulated more label than cerebral cortex, hippocampus, or cerebellum (Borowitz et al. 1994). Similarly, Baskin et al. (1987) found that the left ventricle of the guinea pig heart contained nearly twice as much as the right ventricle after a brief exposure to cyanide. Binding to certain tissue constituents may be important for decreasing the actions of cyanide and protecting cells from cyanide toxicity (Devlin et al. 1989b).

Storage. Cyanide does not accumulate in blood and tissues following chronic oral exposure. In a study with rats administered hydrogen cyanide in the diet at $\approx$10.4 mg CN$^-$/kg/day for 2 years, virtually no cyanide was found in plasma or kidneys (Howard and Hanzal 1955).

Excretion. Cyanide metabolites (of which thiocyanate is the major component) are excreted primarily in urine, with small amounts of the metabolites eliminated through the lungs. When radioactively labeled cyanide is administered, most of the radioactivity is detected in the urine within 24 hours (Farooqui and Ahmed 1982; Okoh 1983). Boxer and Richards (1952) were the first to show that cyanide was oxidized to

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CO_2 and in the Okoh (1983) study, about 4% of the radioactivity was expired, mostly as carbon dioxide. See Section 2.3.4 for information on studies examining elimination and excretion.

Effect of Dose and Duration of Exposure on Toxicity. The severity of neurological effects in humans and animals after acute oral exposure to cyanide is dose-related (Chen and Rose 1952; Lasch and El Shawa 1981). Central nervous system effects have been observed following acute-duration exposures (Levine and Stypulkowski 1959a) and chronic-duration exposures (Hertting et al. 1960), via the inhalation and oral routes. Necrosis is the most prevalent central nervous system effect following acute-duration exposure to high concentrations of cyanide, whereas demyelination is observed in animals that survive repeated exposure protocols (Bass 1968; Ibrahim et al. 1963).

Increased duration of exposure to inhaled cyanide in mice resulted in lower LC_{50} values (Higgins et al. 1972; Matijak-Schaper and Alarie 1982). Additionally, cyanide toxicity was influenced by dilution of the gavage dose. Greater dilution resulted in higher mortality for the same total dose (Ferguson 1962).

Tylleskar et al. (1992) studied a population in rural Zaire that was affected with Konzo. Konzo is characterized by symmetric isolated bilateral involvement of upper motor neurons of abrupt onset; the damage is permanent but not progressive. The Konzo patients had serum thiocyanate concentrations below those of the controls. The authors suggest that the combination of high exposure and a decreased conversion rate because of a deficiency in suitable sulfur substrates might explain this difference. Thus, daily exposure and decreased conversion rates may lead to high blood concentrations of cyanide that may lead to upper motor neuron damage. It has been suggested that defects in the metabolic conversion of cyanide to thiocyanate, as well as nutritional deficiencies of protein and vitamin B_{12} play a role in the development of central nervous system disorders such as tropical ataxic neuropathy, tobacco amblyopia, and Leber's hereditary optic atrophy.

Route-Dependent Toxicity. A great similarity exists among cyanide-induced effects following inhalation, oral, and dermal exposure. Signs of toxicity in target organs from acute cyanide exposure (primarily central nervous system and heart), and chronic exposure (including central nervous system and thyroid gland), are similar in both humans and animals regardless of route.

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2.4.2 Mechanisms of Toxicity

Effects of Metabolism on Toxicity. Cyanide (as hydrogen cyanide), originating *in vivo* by dissociation of potassium cyanide, sodium cyanide, and other cyanogenic compounds or arising from catabolism of cyanogenic glycosides, exerts its acute toxic effects by complexing with the ferric iron atom in metalloenzymes, resulting in histotoxic anoxia through inhibition of cytochrome c oxidase (DiPalma 1971; Way 1984), metalloenzymes which function as the terminal oxidase of the inner mitochondrial membrane respiratory chain. A two-step process has been proposed: cyanide as hydrogen cyanide first penetrates a protein crevice of cytochrome c oxidase and binds to the protein (Stannard and Horecker 1948). Hydrogen cyanide then binds to the trivalent iron ion of the enzyme, forming a relatively stable (but reversible) coordination complex. One mole of hydrogen cyanide is bound to one mole of cytochrome $\underline{c}$ oxidase (Van Buuren et al. 1972). As a result, the enzyme becomes unable to catalyze the reactions in which electrons would be transferred from reduced cytochrome to oxygen. Cellular oxygen utilization is thus impaired, with resultant reduction in or cessation of aerobic metabolism (Rieders 1971; Way 1984). Glucose catabolism then shifts from the aerobic pathway to anaerobic metabolism including the pentose phosphate pathway, resulting in increased blood glucose, pyruvic acid, lactic acid, and nicotinamide adenine dinucleotide (NADPH) levels, and a decrease in the adenosine triphosphate/adenosine diphosphate (ATP/ADP) ratio (Rieders 197 1; Way 1984). Wilson et al. (1994) suggest that it is the binding of cyanide to oxidized Cu_B in an enzyme containing a single electron that leads to the inhibition of cytochrome $\underline{c}$ oxidase.

The inhibition of oxygen use by cells (termed histoxic hypoxia) causes oxygen tensions to rise in peripheral tissues (Smith 1996). This results in a decrease in the unloading gradient for oxyhemoglobin; thus, oxyhemoglobin is carried in the venous blood (Rieders 1971). Inhibition of oxygen utilization is thought to occur rapidly after cyanide exposure. Tadic (1992) determined that inhibition of cytochrome $\underline{c}$ oxidase activity in rat brains was most pronounced between 15 and 20 minutes after administration of sodium cyanide (12 mg/kg or $1.3xLD_{50}$). In addition to binding to cytochrome c oxidase, cyanide also binds to catalase, peroxidase, methemoglobin, hydroxocobalamin, phosphatase, tyrosinase, ascorbic acid oxidase, xanthine oxidase, and succinic dehydrogenase. These reactions may also contribute to the classic signs of cyanide toxicity (Ardelt et al. 1989; DiPalma 1971; Rieders 1971). Information on mechanisms of toxicity in target organs is presented below.

Target Organ Toxicity. The central nervous system is the primary target for cyanide toxicity in humans and animals. Acute inhalation of high concentrations of cyanide provokes a brief central nervous

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system stimulation followed by depression, convulsions, coma, and death in humans (Bonsall 1984; Chen and Rose 1952; Peden et al. 1986; Potter 1950; Singh et al. 1989) and in animals (Haymaker et al. 1952; McNerney and Schrenk 1960; Purser et al. 1984). The effects are probably due to rapid biochemical changes in the brain, such as changes in ion flux, neurotransmitter release, and possibly peroxide formation (Johnson and Isom 1985; Kanthasamy et al. 1991a, 1994; Persson et al. 1985). In both in viva and *in vitro* studies using brain tissue, the sensitivity of mitochondrial cytochrome c oxidase activity to inhibition by cyanide was greater than the inhibition of mitochondrial respiratory activity. Only after cytochrome c oxidase activity was depressed by >50% was a large decrease in respiratory activity detected, suggesting that a large portion of cytochrome c oxidase may serves as a functional reserve. Cyanide poisoning likely involves mechanisms in addition to inhibition of cytochrome c oxidase activity (Pettersen and Cohen 1993). Cyanide is a strong nucleophile with multiple effects including release of secondary neurotransmitters, release of catecholamines from adrenal glands and adrenergic nerves, and it inhibits antioxidant enzymes in the brain (Smith 1996). However, the extremely low concentration of cyanide required to inhibit the oxidase, the rapid interaction of hydrogen cyanide with the enzyme and the key role of cytochrome c oxidase in aerobic metabolism all combine to make cyanide inhibition of the terminal step of electron transport (Chance and Erecinsk 1971; Gibson and Greenwood 1963) the key molecular target in cyanide poisoning.

Inhalation and oral studies in animals have shown that cyanide exposure leads to encephalopathy in both white and gray matter. In particular, damage has been observed in regions such as the deep cerebral white matter, the corpus callosum, hippocampus, corpora striata, pallium, and substantia nigra. White matter may be more sensitive because of its relatively low cytochrome c oxidase content. Rats treated with a single dose of sodium cyanide subcutaneously developed necrotic lesions of the corpus callosum and optic nerve (Lessell 1971). High mortality was observed among exposed animals. These effects have been observed following acute-duration exposures (Levine and Stypulkowski 1959a) and chronic-duration exposures (Hertting et al. 1960). Necrosis is a prevalent central nervous system effect following acute exposure to high concentrations of cyanide, whereas demyelination is observed in animals that survive repeated exposure protocols (Bass 1968; Ibrahim et al. 1963). The mechanism of cyanide-induced demyelination is not completely understood, but the evidence suggests that a direct effect of cyanide on white matter may not be necessary. It has been suggested that local edema affecting the oligodendrocytes and caused by vascular changes triggered by cyanide represent a primary event in demyelination (Bass 1968; Ibrahim et al. 1963). Aiken and Braitman (1989) determined that cyanide has a direct effect on neurons not mediated by its inhibition of metabolism. Consistent with the view that cyanide toxicity is due to the inability of tissue to utilize oxygen is a report that in cyanide-intoxicated rats, arterial pO_2

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levels rose, while carbon dioxide levels fell (Brierley et al. 1976). The authors suggested that the low levels of carbon dioxide may have led to vasoconstriction and reduction in brain blood flow; therefore, brain damage may have been due to both histotoxic and anoxic effects. Partial remyelination after cessation of exposure has been reported, but it is apparent that this process, unlike that in the peripheral nervous system, is slow and incomplete (Hirano et al. 1968). The topographic selectivity of cyanideinduced encephalopathy may be related to the depth of acute intoxication and distribution of blood flow, which may result in selected regions of vascular insufficiency (Levine 1969).

Several recent studies have suggested that a disruption in neuronal calcium regulation may be an important factor in the manifestation of cyanide-induced neurotoxic events following acute exposure. The predominance of anaerobic metabolism in a cyanide-poisoned cell decreases the ATP/ADP ratio, or energy charge (Isom et al. 1975), and thus alters energy-dependent processes such as cellular calcium homeostasis (Johnson et al. 1986). Elevated levels of intracellular calcium in a cyanide-exposed, presynaptic squid neuron were observed in an *in vitro* study (Adams et al. 1985). Elevated levels of neuronal calcium may initiate release of neurotransmitters from the presynaptic terminal, which can activate the nervous system (Maduh et al. 1990a). Levels of whole-brain calcium increased when potassium cyanide was administered subcutaneously to mice. These increases were correlated with cyanide-induced tremors (Johnson et al. 1986). Brain injury may be associated with cyanide-induced endogenous glutamate release, mediated by both calcium dependent and independent mechanisms, which in turn produce excitotoxic responses in select brain areas (Pate1 et al. 1991, 1992, 1993). In examining receptor subtypes involved in mediating cyanide-induced toxicity, sodium cyanide-induced cytotoxicity was found to be mediated primarily by activation of the N-Methyl-D Aspartate (excitatory amino acid) receptor. Strum et al. (1993) examined the ability of adenosine to attenuate the excitotoxicity secondary to glutamate receptor activation following potassium cyanide exposure in hippocampal neuronal cell cultures. The authors concluded that neuronal cell death was mediated at least in part by glutamate and that the cell death was attenuated by adenosine via the A_1-specific mechanism. Increases in intracellular calcium have also been associated with cyanide induced effects on vascular smooth muscle and cardiac muscle, possibly inducing cell damage (Allen and Smith 1985; Robinson et al. 1985a). These effects may result from ischemia-induced increases in extracellular potassium, which in turn enhance cellular permeabilities to calcium (Robinson et al. 1985b). Furthermore, changes in cytosolic pH and dysfunction of hydrogen ion handling mechanisms were observed in neuronal cells exposed *in vitro* to cyanide (Maduh et al. 1990b). Pazdemik et al. (1994) reported a global reduction of local cerebral glucose utilization (LCGU) in almost every region of the brain after sublethal exposure to sodium cyanide. These results support the expectation that cyanide

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causes a shift from aerobic to anaerobic metabolism, as illustrated by increases in extracellular lactate and pyruvate and in LCGU.

When cyanide blocks oxidative metabolism in mitochondria, cells shift their metabolism and enhanced glucose utilization occurs. One consequence of this altered metabolic pattern is accumulation of nicotinamide adenine dinucleotide (NADH). NADH is a powerful stimulant of calcium mobilization from cell stores through "inositol triphosphate receptors." Elevated calcium damages cells. Increase in cellular NADH, therefore, is an important event in the toxic action of cyanide (Kaplin et al. 1996).

Recent studies have shown that cyanide releases catecholamines from rat pheochromocytoma cells and brain slices (Kanthasamy et al. 1991 b), from isolated bovine adrenal glands (Borowitz et al. 1988), and from adrenals of mice following subcutaneous injection of high doses of potassium cyanide (Kanthasamy et al. 1991b). Thus, it was proposed that the cardiac and peripheral autonomic responses to cyanide are partially mediated by an elevation of plasma catecholamines (Kanthasamy et al. 1991b). Dopamine levels in potassium cyanide-treated animals were significantly decreased in striatum and hippocampus, and somewhat decreased in cerebral cortex of mice (Kanthasamy et al. 1994), while extracellular levels of dopamine and homovanillic acid were increased in the brain of rats treated with sodium cyanide (Cassel et al. 1995). Kiuchi et al. (1992) suggested that suppression of ATP production by sodium cyanide induces an abrupt and remarkable increase in dopamine release from the nerve terminal in the striatum. Kanthasamy et al. (1994) also observed that in striatal and hippocampal tissues, but not in cerebral cortex, malondialdehyde levels increased indicating the occurrence of lipid peroxidation in these brain regions. In addition, reduced numbers of tyrosine hydroxylase (TH) positive cells indicated a loss of dopaminergic neurons (Kanthasamy et al. 1994). Behavioral effects seen in the mice were reversed by administration of I-DOPA (treatment for dopamine-deficiency). Ardelt et al. (1994) also evaluated hydroperoxide generation as a potential mechanism of cyanide neurotoxicity. Increased lipid peroxidation was observed in brain and kidney, but not in liver or heart. It was also determined that calcium plays a critical role in lipid peroxidation in neuronal cells. Subcellular fractionation of brain tissue showed an increase in lipid peroxidation in the microsomal but not mitochondrial fraction. Matsumoto et al. (1993) evaluated the involvement of extracellular calcium in dopamine release from rat striatum resulting from cyanide exposure. A gradual increase in intracellular calcium was observed during incubation of sodium cyanide with striatal slices. The excessive influx of extracellular calcium during sodium cyanide perfusion may contribute to the changes in dopamine levels in striatum and to the observed suppression of dopamine release in response to high potassium stimulation. Release of dopamine was not suppressed by perfusion with a calcium-free solution; thus, additional mechanisms other than the opening of calcium channels

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must also be involved in dopamine release by cyanide. Decreased dopamine uptake has been suggested as an explanation for this increase in dopamine, since dopamine uptake is driven by a sodium gradient which is maintained by the Na/K ATPase and could be reduced if ATP is depleted. Cyanide did not affect monamine oxidase or catechol-o-methyl transferase, suggesting that a disturbance in dopamine metabolism did not lead to extracellular dopamine elevation (Matsumoto et al. 1993).

Cassel et al. (1994) examined the *in vitro* effects of sodium cyanide on two forms of monoamine oxidase (MAO), an enzyme important in regulation of biogenic amines in the brain and peripheral tissue. In striatal tissue, cyanide produced a dose-dependent increase in the activity of MAO-A but not MAO-B. Greer and Carter (I 995) investigated the effects of hydrogen cyanide on the neural mechanisms controlling breathing. Cyanide, at concentrations considered lethal *in vivo*, caused a modest depression of the frequency and amplitude of inspiratory rhythmic discharge. The neuronal network underlying respiration continued to function for hours in the presence of very high concentrations of cyanide. The authors hypothesized that the rapid suppression of breathing caused by cyanide *in vivo* is due to changes in neuronal excitability in respiratory centers in the central nervous system, rather than due to cellular metabolism of neurons within respiratory centers.

Results of *in vitro* studies suggest an interaction between calcium ions and cyanide in cardiovascular effects (Allen and Smith 1985; Robinson et al. 1985a). It has been demonstrated that exposure to cyanide in metabolically depleted ferret papillary muscle eventually results in elevated intracellular calcium levels, but only after a substantial contracture develops (Allen and Smith 1985). The authors proposed that intracellular calcium may precipitate cell damage and arrhythmias. The mechanism by which calcium levels are raised was not determined. Franchini and Krieger (1993) produced selective denervation of the aortic and carotid bifurcation areas, and confirmed the carotid body chemoreceptor origin of cardiovascular, respiratory and certain behavioral responses to cyanide in rats. Bradycardia and hyperventilation induced by cyanide are typical responses evoked by carotid body chemoreceptor stimulation (Franchini and Krieger 1993).

The respiratory effects of cyanide include dyspnea, asphyxia, and a decrease in respiratory rate (Blanc et al. 1985; Matijak-Schaper and Alarie 1982: McNerney and Schrenk 1960). A recent study (Bhattacharya et al. 1994) demonstrated increased air flow, transthoracic pressure, and tidal volume accompanied by a significant decrease in pulmonary phospholipids following inhalation of hydrogen cyanide in rats. This study also showed that hydrogen cyanide exhibited a direct effect on pulmonary cells in rats.

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Cyanide-induced effects on the thyroid gland are particularly important in chronic cyanide exposures and are discussed in several studies. Thiocyanate markedly inhibits accumulation of iodine by the thyroid gland, thus decreasing the ability of the gland to maintain a concentration of iodine above that of blood (VanderLaan and Bissell 1946). In addition, thiocyanate may inhibit the iodination process, thus interfering with the binding of glandular iodine and reducing the formation of thyroxine (Et-mans et al. 1972). Changes in thyroid chemistry reported in individuals chronically exposed to cyanide have not been accompanied by manifestations of hypothyroidism. Fukayama et al. (1992) studied the antithyroid action of thiocyanate in a culture system of thyroid follicles. Thiocyanate concentrations equivalent to serum levels in smokers showed three independent antithyroid actions, including inhibition of iodide transport, inhibition of binding of iodide in the thyroid, and increased iodide efflux. The discrepancy in the potency of the antithyroid activity of thiocyanate *in vivo* and *in vitro* appears to be due to the presence of iodide and pseudohalogens known to alter the effect of thiocyanate on the thyroid (Van Middlesworth 1986).

Persons with a metabolic disturbance in the conversion of cyanide to thiocyanate may be at greater risk from the toxic effect of cyanide. A defect in the rhodanese system and vitamin B l2 deficiency have been noted in persons with tobacco amblyopia and Leber's hereditary optic atrophy exposed to tobacco smoke which contains cyanide (Wilson 1983). Iodine deficiency, along with excess chronic exposure to cyanide, may in certain cases be involved in the etiology of such thyroid disorders as goiter and cretinism (Delange and Ermans 1971; Ermans et al. 1972). Also, protein deficiencies and vitamin B,, and riboflavin, and other deficiencies may subject people who eat foods high in cyanogenic glycosides to increased risk of neuropathies (Makene and Wilson 1972; Osuntokun 1972; Osuntokun et al. 1969). Patients with motor neuron disease (amyotrophic lateral sclerosis) possess a disorder in cyanide metabolism that may result in higher susceptibility to cyanide (Kato et al. 1985).

Carcinogenesis. No studies were located regarding carcinogenic effects of cyanide exposure in humans or animals following any route of exposure. Therefore, no mechanism of carcinogenesis can be discussed.

2.4.3 Animal-to-Human Extrapolations

Biological effects of cyanide in humans have been demonstrated (Smith 1996; Wexler et al. 1947). However, no studies directly comparing the cytotoxicity of similar animal and human cells were available. However, a difference in species susceptibility to cyanide poisoning was indicated by slightly lower lethal concentrations in rabbits compared to rats (Ballantyne 1983a). Additionally, mortality varied depending

on the cyanide compound used. In the Ballantyne (1983a) study, dermal application resulted in cyanide levels in blood and serum that were lower after topical sodium cyanide and potassium cyanide exposure than from hydrogen cyanide; however, oral exposure in rabbits produced an LD_{50} of 2.3-2.7 mg CN^{-}/kg/day, regardless of whether the source was hydrocyanic acid, sodium cyanide, or potassium cyanide (Ballantyne 1983a).

Species and tissue distribution of rhodanese, an enzyme important in metabolizing cyanide, is highly variable (Himwich and Saunder 1948). In dogs, the highest activity of rhodanese was found in the adrenal gland, ≈ 2.5 times greater than the activity in the liver. Monkeys, rabbits, and rats had the highest rhodanese activity in liver and kidney, with relatively low levels in adrenals. It should be noted that total rhodanese activity in other species was higher than in dogs, which is consistent with the greater susceptibility of dogs to the acute effects of cyanide. Thus, dogs may not be a good model from which to extrapolate the toxicity of cyanide to humans. Similar activities of the enzyme among the species were found for the brain, testes, lungs, spleen, and muscle.

2.5 RELEVANCE TO PUBLIC HEALTH

Overview

Data are available regarding health effects in humans and animals after inhalation, oral, and dermal exposure to cyanide. Cyanide is a highly toxic chemical that can produce death in humans and animals rapidly. This characteristic has long been recognized and, therefore, cyanide has often been used with suicidal and homicidal intent, and as a chemical warfare agent. Of the cyanide compounds, hydrogen cyanide, sodium cyanide, and potassium cyanide are the most common ones in the environment, with gaseous hydrogen cyanide being present in air. Cyanide can be formed during some chemical processes used in industry (for further information see Chapter 4). Thiocyanate is a metabolite of cyanide formed in the body from exposure to cyanide compounds. Dietary sources of cyanide include plants that contain cyanogenic glycosides such as cassava root (tapioca), lima beans, soy, spinach, and certain fruit pits and juices. However, in the United States, cyanide exposure from dietary sources is usually not of concern since the amount of cyanide contained in these sources is very low.

Sufficient concentrations of cyanide cause histotoxic hypoxia in the organism. The toxicity is due to the inability of the tissues to use oxygen. Due to this effect, oxygen tension is usually high in victims of cyanide poisoning. The primary target organs for acute cyanide toxicity are the central nervous system

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and the heart. Signs of toxicity in acute cyanide poisoning are tachypnea, incoordination of movements, cardiac irregularities, convulsions, coma, respiratory failure, and death. These effects are common to both humans and animals. Furthermore, a great similarity exists among cyanide-induced effects following inhalation, oral, and dermal exposure. The target organs of chronic cyanide toxicity are the central nervous system, reproductive system, and thyroid gland. No definitive studies were located regarding developmental and reproductive effects in humans after exposure to cyanide or ingestion of foods containing cyanogenic plant material. However, oral studies in animals indicate possible developmental toxicity. No studies were located regarding carcinogenic effects of cyanide.

Minimal Risk Levels for Cyanide

Inhalation MRLs

No acute-, intermediate-, or chronic-duration inhalation MRLs were derived for cyanide because of the limitations associated with the available studies. Many of the animal and human studies used lethality, or serious effects, such as coma, as the end point. Two epidemiological studies are available; however, one study lacked good exposure data, and the other study involved occupational exposure in the electroplating industry where exposure to other chemicals may have occurred.

Oral MRLs

An acute oral MRL was not derived for cyanide because most of the available studies reported lethality as an end point, and there is a lack of information regarding acute systemic effects in animals.

- An MRL of 0.05 mg/kg/day has been derived for intermediate-duration (15-364 days) oral exposure to cyanide.

This MRL was derived from a NOAEL of 4.5 mg/kg/day in a study in which groups of 10 male and 10 female rats were given 0,0.2,0.5, 1.4 (males), 1.7 (females), 4.5 (males), 4.9 (females), or 12.5 mg/kg/day cyanide in the drinking water for 13 weeks, as sodium cyanide (NTP 1993). At the end of the study, the animals were evaluated for histopathology, clinical chemistry, urine chemistry, and reproductive toxicity. A number of reproductive effects, such as decreases in left epididymis weight, left cauda epididymis weight, left testis weight, spermatid heads, and spermatid counts were observed at 12.5 mg/kg/day. At 1.4 and 4.5 mg/kg/day, significantly decreased weight of the left cauda epididymis

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and spermatozoa motility were observed; however, these effects alone were not considered to be adverse. For females, more time was spent in the proestrus and diestrus stages, and less time in estrus and metestrus stages in the 4.9 and 12.7 mg/kg/day dose groups; however, this was considered to be a minimal effect. The 12.5 mg/kg/day dose was identified as the LOAEL, based on all the reproductive effects observed in male rats, and the 4.5 mg/kg/day dose was identified as the NOAEL. This NOAEL was used with an uncertainty factor of 100 (10 for extrapolation of animals to humans and 10 for human variability) to derive an MRL. It is important to note that this MRL was based on a study using sodium cyanide, which is a soluble form of cyanide. In addition, a LOAEL of 1.04 mg/kg/day based on systemic and reproductive effects in dogs was identified (Kamalu 1993). However, this study was not used to derive the intermediate oral MRL because dogs are not a good model for human toxicity because dogs have very low levels of rhodenase, an enzyme which is used to detoxify cyanide.

A chronic oral MRL was not derived because of the limitations of the available studies. Human studies that described dietary exposure to cyanide through consumption of cassava lacked quantitative exposure information. The one available chronic oral study in rats found no treatment related effects (Howard and Hanzel 1955).

Death. The signs of cyanide toxicity at concentrations leading to death in humans are well described. Intoxication at $\geq$ 2,000 ppm hydrogen cyanide is characterized by a brief sensation of dryness and burning in the throat due to local irritation, a suffusing warmth, and a hunger for air (Rieders 1971). Hyperpnea, and sometimes a brief outcry, follows the first breath. In less than one minute, apnea, a few gasps, collapse, and convulsions occur. Cardiovascular failure may also occur, although the heart may continue to beat for 3-4 minutes after the last breath. Reported signs include a rose-colored hue of the skin and a bitter almond-like odor on the breath. The total absorbed dose of hydrogen cyanide in such rapid deaths can be as low as 0.7 mg/kg. Similar signs were reported following ingestion of high doses of cyanide salts. Within a few minutes after swallowing the toxicant, the victim collapses, frequently with a scream (Gettler and St. George 1934). Dyspnea, convulsions, and death from asphyxia follow. Dermal exposure to cyanide results in comparable effects. Based on case report studies, LC_{50} values for humans were estimated for inhalation (McNamara 1976, as cited in Ballantyne 1987), oral (EPA 1987a), and dermal (Rieders 1971) routes as 524 ppm, 1.52 mg/kg, and 100 mg/kg, respectively.

In general, signs of toxicity preceding death are the same in humans and animals. Dyspnea, convulsions, and asphyxiation occur in animals following all routes of exposure to cyanide. LC_{50} values were provided for inhalation of hydrogen cyanide in rats (Ballantyne 1983a; Higgins et al. 1972), mice (Higgins et al.

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1972; Matijak-Schaper and Alarie 1982), and rabbits (Ballantyne 1983a). Lethal concentrations were also reported in dogs (Haymaker et al. 1952; Valade 1952). Lower cyanide concentrations required longer periods of exposure to produce death. The difference in species susceptibility to cyanide poisoning was indicated by lower lethal concentrations in rabbits compared with rats.

Following oral exposure in animals, LD_{50} values were calculated for rats dosed with cyanide as sodium cyanide (Ballantyne 1988; Smyth et al. 1969) and in rabbits treated with cyanide as hydrogen cyanide, sodium cyanide, and potassium cyanide (Ballantyne 1983a). However, the LD_{50} value from the Ballantyne (1988) study is not considered reliable since the animals were starved, and thus physiologically compromised. For oral exposure, the molar lethal toxicities of hydrogen cyanide, sodium cyanide, and potassium cyanide are similar. Rabbits appeared to be more susceptible to the lethal toxicity of these three compounds than were rats (Ballantyne 1988). Cyanide toxicity was influenced by dilution of gavage doses. The higher the dilution, the higher the mortality for the same total dose.

Deaths can occur after dermal exposure to hydrogen cyanide, sodium cyanide, or potassium cyanide (Ballantyne 1983a). The lowest LD_{50} indicating the highest toxicity, was calculated for cyanide applied to the skin in the form of hydrogen cyanide. Potassium cyanide was the least toxic compound. A similar pattern in cyanide toxicity was observed among these three compounds when applied into the inferior conjunctival sac of rabbits (Ballantyne 1983a, 1983b). Dermal absorption and consequent mortality were also observed in guinea pigs (Fairley et al. 1934; Walton and Witherspoon 1926) and in dogs (Walton and Witherspoon 1926) following unspecified doses of hydrogen cyanide. Cyanide absorption and, therefore, toxicity differed in rabbits with dry intact, moist, or abraded skin (Ballantyne 1988), as expected. The lowest LD_{50} for cyanide given as sodium cyanide was calculated for rabbits with abraded skin.

Cyanide can inhibit enzymatic activity by binding to the metallic cofactor in metalloenzymes. Cytochrome c oxidase (an enzyme in the mitochondrial respiratory chain) is sensitive to cyanide action (Way 1984). Due to its inhibition, oxygen cannot be utilized, histotoxic hypoxia develops, and this can lead to deaths of humans and animals (see Section 2.3.3).

The inhibition of oxygen use by cells causes oxygen tensions to rise in peripheral tissues; this results in a decrease in the unloading gradient for oxyhemoglobin. Thus, oxyhemoglobin is carried in the venous blood (Rieders 1971). Inhibition of oxygen utilization is thought to occur rapidly after cyanide exposure. Inhibition of cytochrome G oxidase activity peaked 3-10 minutes following the intraperitoneal administration of potassium cyanide to mice, rats, and gerbils (Schubert and Brill 1968).

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In addition to binding to cytochrome c oxidase, cyanide inhibits catalase, peroxidase, methemoglobin, hydroxocobalamin, phosphatase, tyrosinase, ascorbic acid oxidase, xanthine oxidase, and succinic dehydrogenase activities. These reactions may make contributions to the signs of cyanide toxicity (Ardelt et al. 1989; Rieders 1971). Signs of cyanide intoxication include an initial hyperpnea followed by dyspnea and then convulsions (Rieders 1971; Way 1984). These effects are due to initial stimulation of carotid and aortic bodies and effects on the central nervous system. Death is caused by respiratory collapse resulting from central nervous system toxicity.

The inorganic cyanides and their cyanohydrins are highly toxic chemicals that should be handled only by properly trained personnel, with appropriate protective equipment, using extreme caution. Death can result from exposure by all routes that humans are likely to experience, including transocular. Although cyanides are among the most acutely toxic of all industrial chemicals, they are produced in large quantities, and are used in many applications; however, they have caused few serious accidents or deaths (Hartung 1982). This appears to be due to the fact that it is common knowledge that the cyanides are very toxic materials that need to be treated with due caution.

Systemic Effects

Respiratory Effects. Respiratory effects commonly occur after inorganic cyanide poisoning by any route of exposure. Following inhalation, the first breath of a lethal concentration of hydrogen cyanide causes hyperpnea (Rieders 1971). The victims experience shortness of breath that may be rapidly (>l minute) followed by apnea. Dyspnea was reported in patients who survived acute inhalation exposure to cyanide (Chen and Rose 1952; Peden et al. 1986; Potter 1950). Similarly, dyspnea was observed in humans following acute oral exposure to cyanide as sodium cyanide (Grandas et al. 1989), as potassium cyanide (Goodhart 1994; Liebowitz and Schwartz 1948; Saincher et al. 1994), or as cyanogenic glycosides in apricot pits (Lasch and El Shawa 1981). Likewise, dyspnea occurred following dermal exposure to cyanide as copper cyanide (Dodds and McKnight 1985) and potassium cyanide (Trapp 1970) in occupational accidents. l&mans acutely exposed to cyanogen experienced nasal irritation (McNerney and Schrenk 1960).

Various symptoms indicating respiratory effects were reported in humans exposed to hydrogen cyanide or its salts in occupational settings. Upper respiratory irritation, cough, altered sense of smell, nasal congestion, epistaxis, hemoptysis, and dyspnea were among the clinical signs of cyanide toxicity (Blanc et al. 1985; Chandra et al. 1980; El Ghawabi et al. 1975). The severity of these effects correlated with

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cyanide levels in workplace air. It must be pointed out, however, that in occupational settings such as electroplating operations or gold recovery, exposure to other chemicals also occurs.

Exposure to inorganic cyanide, its salts, or cyanohydrins by any route produces similar respiratory effects in animals.

Cardiovascular Effects. Hypotension was the main effect reported in patients after acute inhalation exposure to hydrogen cyanide (Chen and Rose 1952; Peden et al. 1986), as well as after oral exposure to potassium cyanide (Liebowitz and Schwartz 1948) or after ingestion of cyanogenic glycosides in apricot pits (Lasch and El Shawa 198 1). Palpitations were recorded in men exposed dermally to hydrogen cyanide (Drinker 1932). Peripheral vasoconstriction and gross plasma extravasation were found in a man whose whole body was exposed to liquid copper cyanide in a cistern (Dodds and McKnight 1985). In many of these cases, the effects reported may reflect an indirect action mediated by the nervous system. Most individuals experienced marked sinus irregularities and a slowing of heart rate immediately after an intravenous injection of cyanide as sodium cyanide (Wexler et al. 1947). Workers exposed to cyanide during electroplating and silver-reclaiming jobs complained of precordial pains (Blanc et al. 1985; El Ghawabi et al. 1975). During electroplating operations, however, exposure to other chemicals such as cleaners and cutting oils also occurs.

Acute inhalation of hydrogen cyanide resulted in bradycardia, arrhythmia, and T-wave abnormalities (Purser et al. 1984), and increased cardiac-specific creatinine phosphokinase activity (O'Flaherty and Thomas 1982) in monkeys. Isolated strips of aorta from rabbits, dogs, and ferrets were used to determine the effects of cyanide on vascular smooth muscle (Robinson et al. 1985b). Cyanide caused small contractions in the isolated rabbit aorta at low cyanide concentrations; at higher cyanide concentrations, relaxation occurred. It was found that chlorpromazine or 4,4'-diisothiocyano-2, 2'-stilbene disulfonic acid (DIDS) reduced the contractions (Robinson et al. 1985a).

Results of *in vitro* studies suggest that both calcium ions and cyanide are involved in cardiovascular effects. It has been demonstrated that exposure to cyanide in a metabolically depleted ferret papillary muscle eventually results in elevated intracellular calcium levels, but only after a substantial contracture develops (Allen and Smith 1985). The authors proposed that intracellular calcium may precipitate cell damage and arrhythmias. The mechanism by which calcium levels are raised was not determined.

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Gastrointestinal Effects. Information regarding gastrointestinal effects after inhalation and dermal exposure to cyanide is limited. Nausea and vomiting were reported in workers exposed to cyanide (Blanc et al. 1985; El Ghawabi et al. 1975). Similarly, exposure to hydrogen cyanide caused vomiting in dogs (Valade 1952). The only information on dermal exposure was provided in a study with guinea pigs (Fairley et al. 1934). Exposure to hydrogen cyanide produced submucous hemorrhages in the stomach.

Following oral exposure, the recorded effects included vomiting in patients after acute exposure to cyanogenic glycosides in apricot pits (Lasch and El Shawa 1981) and in a man who ingested 7.6 mg CN-/kg in a suicide attempt (Goodhart 1994), gastrointestinal spasms after exposure to cyanide in the form of potassium cyanide (Thomas and Brooks 1970), and gastric necrosis after ingestion of sodium cyanide (Grandas et al. 1989). Furthermore, frequent vomiting was observed in pigs orally exposed to low doses of cyanide as potassium cyanide; however, the animals were experimentally compromised as they were starved (Jackson 1988).

Gastrointestinal effects can be caused by central nervous system stimulation (nausea) or by direct contact (necrosis) with cyanide salts.

Hematological Effects. No pathological changes were found during hematological examinations of an individual following ingestion of 15 mg CN⁻/kg as potassium cyanide (Liebowitz and Schwartz 1948). However, increased hemoglobin and lymphocyte counts were found in workers occupationally exposed to 6.4-10.4 ppm cyanide (El Ghawabi et al. 1975). It is possible, however, that chemicals other than cyanide may have contributed to the effects observed in occupationally exposed subjects. In another study (Kumar et al. 1992), an increase in neutrophil values, an increase in erythrocyte sedimentation rate, and a decrease in hemoglobin levels were noted in male workers exposed to unspecified concentrations of cyanide during case hardening and electroplating.

Increases in the mean corpuscular volume of erythrocytes and of hemoglobin concentration suggested hematological effects in rats after exposure to potassium silver cyanide for 90 days (Gerhart 1987b). Decreased hematocrit, erythrocyte count, and hemoglobin concentration were found in rats treated with copper cyanide by gavage during intermediate-duration exposure; however, because of the known hematotoxic properties of copper, these effects could be attributed mainly to copper (Gerhart 1987a). Minimal changes were observed in hematology in rats and mice exposed to sodium cyanide in the drinking water for 13 weeks, and the authors did not consider them to be treatment related (NTP 1993).

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Musculoskeletal Effects. Convulsions are typical symptoms of cyanide poisoning after inhalation (Rieders 1971), oral (Gettler and St. George 1934; Haymaker et al. 1952), or dermal exposure (Ballantyne 1988; Fairley et al. 1934; Walton and Witherspoon 1926). The convulsions indicate involvement of the central nervous system. Furthermore, muscular rigidity was reported after acute inhalation (Haymaker et al. 1952) and oral (Grandas et al. 1989; Saincher et al. 1994) exposure to high levels of cyanide. Skeletal muscle participates significantly in cyanide biotransformation *in vitro* (Devlin et al. 1989a). In muscles sectioned longitudinally, points of rhodanese staining were associated with mitochondria within the fiber. Cyanide clearance in isolated hind limbs of rats was only 1.5 times lower than in the liver (Devlin et al. 1989b). Despite the presence of cyanide in muscles, muscular effects observed in cyanide poisoning victims may in part reflect cyanide toxicity to the central nervous system.

Hepatic Effects. No studies were located regarding hepatic effects in humans after exposure to cyanide by the oral and dermal routes. An increase in serum alkaline phosphatase was noted in workers exposed to unspecified levels of cyanide; however, serum bilirubin was found to be within the normal range in workers exposed to unspecified levels of cyanide (Kumar et al. 1992). Limited information was obtained in animals. Increased bilirubin, alkaline phosphatase, SGOT and SGPT levels, necrosis, and decreased globulin levels were found in the blood of male rats that were dosed with cyanide as copper cyanide. However, these effects were probably mainly due to the toxicity of copper (Gerhart 1987a). Changes in absolute and relative liver weights were observed in rats and mice exposed to sodium cyanide in the drinking water for 13 weeks, but they were minor and sporadic, and the authors did not consider them to be treatment related (NTP 1993). Periportal vacuolation and congestion were observed in the liver of dogs fed cassava, while no hepatic effects were observed in dogs fed rice with sodium cyanide added (Kamalu 1993). No hepatic effects were found in rats gavaged with potassium silver cyanide for the same time period (Gerhart 1987b) or in rats fed for 2 years with a diet fumigated with hydrogen cyanide (Howard and Hanzal 1955). Furthermore, no effects were seen in rats and monkeys following 6 months of inhalation exposure to 11 ppm cyanogen (6 hours a day, 5 days a week) (Lewis et al. 1984).

In vitro studies indicated that cyanide biotransformation in the liver is high because of the high rhodanese activity in the organ (Devlin et al. 1989a). Cyanide extraction ratios and rates of thiosulfate generation were established in isolated rat livers (Devlin et al. 1989b). Cyanide clearance was $\approx$ 1.5 times greater in liver (calculated for the total mass) as in skeletal muscle. Adding sodium thiosulfate to the system quickly increased the conversion of cyanide to thiocyanate. Interspecies differences in liver rhodanese activity were reported in animals (Drawbaugh and Marrs 1987). The activity was highest in rats, hamsters, and guinea pigs, followed by rabbits, and lowest in marmosets and dogs. This variability can explain

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interspecies differences in sensitivity to cyanide toxicity demonstrated by different LC_{50} values. It is evident that the liver plays an important role in cyanide toxicokinetics and it can be anticipated that, following rhodanese inactivation, harmful effects to liver tissue may be expected.

Renal Effects. No studies were located regarding renal effects in humans after inhalation exposure to cyanide. Case reports cited transitory albuminuria in a man ingesting 15 mg CN^-/kg as potassium cyanide (Liebowitz and Schwartz 1948) and transitory oliguria in a man who accidentally fell into a cistern of copper cyanide (Dodds and McKnight 1985). Few studies cited renal effects in animals following oral exposure. Decreased kidney weight was observed in rats exposed to copper cyanide (Gerhart 1987a) and increased blood urea nitrogen was found in rats exposed to potassium silver cyanide (Gerhart 1987b) in the intermediate-duration experiments. Histopathological changes in glomerular cells were reported in pigs fed cassava roots for 110 days (Tewe and Maner 1981b) and in epithelial tubular cells in dogs exposed to sodium cyanide for 14.5 months (Hertting et al. 1960). Changes in absolute and relative kidney weight were observed in rats and mice exposed to sodium cyanide in the drinking water for 13 weeks, but they were minor and sporadic, and the authors did not consider them to be treatment related (NTP 1993). Vacuolation, swelling, and proximal tubular damage with desquamation of the epithelium and casts were observed in the kidneys of dogs fed cassava, while increased urinary protein, casts, and some desquamation, but no damage to the proximal tubules, were observed in dogs fed rice with sodium cyanide added (Kamalu 1993). However, no kidney effects were observed in rats after chronic oral exposure to hydrogen cyanide (Howard and Hanzal 1955) and in rats and monkeys after intermediate duration inhalation exposure to cyanogen (Lewis et al. 1984). Interspecies differences in rhodanese activity in kidneys were found in several species; the differences were similar to those observed for liver rhodanese activity (Drawbaugh and Marrs 1987). There is no conclusive evidence to support a nephrotoxic action of cyanide.

Endocrine Effects. Thiocyanate is goitrogenic in animals and humans (VanderLaan and Bissell 1946). Although within normal limits, statistically significant increased levels of TSH found in workers exposed to cyanide in a silver-reclaiming facility suggested thyroid effects (Blanc et al. 1985). Furthermore, increased radioactive iodine uptake and enlarged thyroid glands were seen in workers exposed to cyanide during electroplating (El Ghawabi et al. 1975). Exposure to other chemicals such as cleaners and cutting oils also occurs during electroplating operations. High incidences of endemic goiter (Delange and Ermans 1971) and a decreased uptake of radioiodine (Cliff et al. 1986; Delange and Ermans 1971) were associated with chronic oral exposure to cyanogenic glycosides in cassava meals. Similar effects were observed in animals. Significant increases in relative thyroid weight were seen in rats that were exposed orally to

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potassium cyanide for an intermediate-duration period (Philbrick et al. 1979). In addition, thyroid gland hypofunction was reported in pigs treated with cassava (Tewe and Maner 198 1 b) or with potassium cyanide (Jackson 1988) during intermediate-duration exposure.

Mechanisms of cyanide-induced effects on the thyroid gland are discussed in several studies. Thiocyanate markedly inhibits accumulation of iodine by the thyroid gland, thus decreasing the ability of the gland to maintain a concentration of iodine above that of blood (VanderLaan and Bissell 1946). In addition, thiocyanate may inhibit the iodination process, thus interfering with the organic binding of glandular iodine and reducing the formation of thyroxine (Ermans et al. 1972). Changes in thyroid chemistry reported in individuals exposed to cyanide have not been accompanied by manifestations of hypothyroidism.

No studies were located on the effects of cyanide on the adrenal gland in humans. However, effects on the adrenal gland, including swelling, hemorrhage, and fibrosis, were observed in dogs fed cassava, as well as in dogs fed rice with sodium cyanide added (Kamalu 1993).

DermalEffects. Rashes developed in ≈ 42% of exposed workers in a study of cyanide in workers (Blanc et al. 1985). No dermal lesions were observed in rabbits exposed dermally to cyanogen (McNerney and Schrenk 1960) and vascular congestion was reported in guinea pigs exposed to hydrogen cyanide (Fairley et al. 1934). Following oral exposure in animals, discolored inguinal fur was observed in rats exposed to copper cyanide (Gerhart 1987a) and potassium silver cyanide (Gerhart 1987b) for an intermediate-duration period.

Ocular Effects. Acute exposure to cyanogen gas produced eye irritation in volunteers (McNemey and Schrenk 1960). Similarly, chronic exposure to cyanide in the working environment caused eye irritation in exposed individuals (Blanc et al. 1985). In addition, exposure to potassium silver cyanide caused ocular opacity in exposed animals, but corneal opacity is also a sign of excessive exposure to soluble silver salts alone. However, when cyanide was applied to a rabbit's eye, keratitis developed regardless of the chemical form of cyanide used (Ballantyne 1983b).

Body Weight Effects. Decreased body weight was reported in workers occupationally exposed to hydrogen cyanide (Blanc et al. 1985). Weight loss was one of several effects in this particular group of workers who were in poor health due to chronic cyanide exposure, but other chemicals such as cleaners and cutting oils may have contributed to this effect. Decreased weight was recorded in rats after inhalation

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exposure to cyanogen for 6 months (Lewis et al. 1984), and decreased weight gain was found in male rats after intermediate-duration oral exposure to copper cyanide (Gerhart 1987a) and potassium silver cyanide (Gerhart 1987b). The changes in body weight are associated with cyanide toxicity. A dose-dependency was observed in some experiments (Gerhart 1987a). A slight decrease in body weight gain was observed in male rats exposed to sodium cyanide in the drinking water for 13 weeks, but no decrease was seen in female rats or mice of either sex (NTP 1993). In all cases cited above, the effects on body weight were seen only in male animals. No body weight effects were observed in female rats (Gerhart 1987a, 1987b; NTP 1993) or female pigs (Tewe and Maner 1981a) exposed orally for an intermediate-duration period. Therefore, male animals appear to be more susceptible to these effects.

Immunological and Lymphoreticular Effects. No studies were located regarding immunological/lumphoreticular effects in humans or animals after cyanide exposure by any route. Therefore, the potential for cyanide to cause immunological/lymphoreticular effects in humans cannot be assessed.

Neurological Effects. The central nervous system is the primary target for cyanide toxicity in humans and animals. Acute-duration inhalation of high concentrations of cyanide provokes a brief central nervous system stimulation followed by depression, convulsions, coma, and death in humans (Bonsall 1984; Chen and Rose 1952; Peden et al. 1986; Potter 1950; Singh et al. 1989) and in animals (Haymaker et al. 1952; McNerney and Schrenk 1960; Purser et al. 1984; Valade 1952). The effects are probably due to rapid biochemical changes in the brain, such as changes in ion flux, neurotransmitter release, and possibly peroxide formation (Johnson and Isom 1987; Kanthasamy et al. 1991 a; Persson et al. 1985).

Chronic exposure to lower cyanide concentrations in occupational settings causes a variety of symptoms from fatigue, dizziness, headaches (Blanc et al. 1985; Chandra et al. 1988; El Ghawabi et al. 1975) to ringing in the ears, paresthesias of extremities, and syncopes (Blanc et al. 1985), or even hemiparesis and hemianopia (Sandberg 1967). In addition, behavioral changes were reported following prolonged cyanide exposure in humans (Chandra et al. 1988) and in animals (Lewis et al. 1984), and a loss of memory, a decrease in visual acuity, psychomotor ability, and visual learning was reported in workers (Kumar et al. 1993). It is possible, however, that during occupational exposure, such as electroplating operations, chemicals other than cyanide may have contributed to the effects observed.

The severity of neurological effects in humans after acute oral exposure to cyanide are dose-related. The symptoms vary from tremor and headache (Chen and Rose 1952; Lasch and El Shawa 1981) to deep coma

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and death in central respiratory arrest (Lasch and El Shawa 198 1; Thomas and Brooks 1970). Pathological changes that may occur in the central nervous system during acute exposure to high doses may complicate recovery. Severe Parkinsonism was one of the effects noted in four case reports resulting from severe acute oral exposure to cyanide (Carella et al. 1988; Grandas et al. 1989; Rosenberg et al. 1989; Uitti et al. 1985). Chronic exposure to cyanogenic glycosides in certain cassava diets may lead to multiple neuropathies in exposed populations (Howlett et al. 1990; Ministry of Health, Mozambique 1984; Monekosso and Wilson 1966; Money 1958; Osuntokun 1968, 1972; Osuntokun et al. 1969; Tylleskar et al. 1994). Among those observed were hyperreflexia or spastic paraparesis of the extremities, spastic dysarthria, visual and hearing difficulties, and cerebellar signs. In addition, epidemics of Konzo, a neurological disease characterized by the sudden onset of varying degrees of symmetric, isolated, nonprogressive spastic paraparesis, have occurred in Africa and have been associated with high dietary cyanide exposure from "bitter" cassava that was not fully processed due to a shortening of the cassava processing time (Tylleskar et al. 1994). It should be mentioned, however, that a recent study reported the isolation of scopoletin, a potent hypotensive and spasmolytic agent, from cassava roots (Obidoa and Obasi 1991) and it is possible that this substance, which remains in cassava during processing (rather than cyanide), is the etiological agent in the tropical ataxic neuropathy observed among cassava eaters (Obidoa and Obasi 1991).

Depending on the dose of cyanide given to animals, neurological effects of varying severity occurred. Tremors, convulsions, and lethargy were seen in rats treated with potassium silver cyanide for 90 days (Gerhart 1987b). Depressed activity was the only neurological sign found in rats exposed to lower doses of total cyanide given as copper cyanide for the same period (Gerhart 1987a). Myelin degeneration of spinal cord tracts was found in rats treated with potassium cyanide for 11.5 months (Philbrick et al. 1979). Similar to inhalation exposure effects, behavioral changes were found in pigs following intermediateduration oral exposure to cyanide as potassium cyanide; however, the animals were experimentally compromised as they were starved (Jackson 1988). In many studies, however, neurological effects occurred at high cyanide exposure levels. Extensive degenerative changes have been produced experimentally in the brain by cyanide treatment (Haymaker et al. 1952; Hirano et al. 1967; Levine 1969; Levine and Stypulkowski 1959a).

Convulsions and coma were also reported in humans (Dodds and McKnight 1985; Trapp 1970) and in animals (Fairley et al. 1934; Walton and Witherspoon 1926) following acute dermal exposure to cyanide.

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The nervous system is the most sensitive target for cyanide toxicity, partly because of its high metabolic demands. High doses of cyanide can result in death via central nervous system effects, which can cause respiratory arrest. In humans, chronic low-level cyanide exposure through cassava consumption (and possibly through tobacco smoke inhalation) has been associated with tropical neuropathy, tobacco amblyopia, and Leber's hereditary optic atrophy. It has been suggested that defects in the metabolic conversion of cyanide to thiocyanate, as well as nutritional deficiencies of protein and vitamin B_{50} and other vitamins and minerals may play a role in the development of these disorders (Wilson 1965).

Rats treated with a single dose of sodium cyanide subcutaneously developed necrotic lesions of the corpus callosum and optic nerve (Lessell 1971). High mortality was observed among exposed animals. Additional inhalation and oral studies in animals have shown that cyanide exposure leads to encephalopathy in both white and gray matter. In particular, damage has been observed in regions such as the deep cerebral white matter, the corpus callosum, hippocampus, corpora striata, pallium, and substantia nigra. White matter may be more sensitive because of its relatively low cytochrome c oxidase content. These effects have been observed following acute (Levine and Stypulkowski !959a, 1959b) and chronic exposures (Hertting et al. 1960). It appears that necrosis is the most prevalent effect following acute exposure to high concentrations of cyanide, whereas demyelination is observed in animals that survive repeated exposure protocols (Bass 1968; Ibrahim et al. 1963). The mechanism of demyelination is not completely understood, but the experimental evidence suggests that a direct effect of cyanide on white matter may not be necessary. It has been suggested that local edema affecting the olygodendrocytes and caused by vascular changes triggered by cyanide represent a primary event in demyelination (Bass 1968; Ibrahim et al. 1963). One characteristic of cyanide intoxication appears to be the inability of tissues to utilize oxygen. Consistent with this view is a report that in cyanide-intoxicated rats arterial pO_2 levels rose while carbon dioxide levels fell (Brierley et al. 1976). The authors suggested that the low levels of carbon dioxide may have led to vasoconstriction and reduction in brain blood flow; therefore brain damage may have been due to both histotoxic and anoxic effects. Partial remyelination after cessation of exposure has been reported, but it is apparent that this process, unlike the peripheral nervous system, is slow and incomplete (Hirano et al. 1968). The topographic selectivity of cyanide-induced encephalopathy may be related to the depth of acute intoxication and the distribution of the blood flow, which may result in selected regions of vascular insufficiency (Levine 1969).

Several recent studies have suggested that disruption of neuronal calcium regulation may be important in the manifestation of cyanide-induced neurotoxic events following acute exposure. Cyanide decreases the ATP/ADP ratio, or energy charge (Isom et al. 1975), and thus alters energy-dependent processes such as

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cellular calcium homeostasis (Johnson et al. 1986). Elevated levels of intracellular calcium in a cyanide exposed, presynaptic squid neuron were observed in an in vitro study (Adams et al. 1985). Elevated levels of neuronal calcium may initiate release of neurotransmitters from the presynaptic terminal, which can activate the nervous system (Maduh et al. 1990a). Levels of whole-brain calcium increased when potassium cyanide was administered subcutaneously to mice (Johnson et al. 1986). These increases were correlated with cyanide-induced tremors (Johnson et al. 1986). Increases in intracellular calcium have also been associated with cyanide-induced effects on vascular smooth muscle and cardiac muscle, possibly inducing cell damage (Allen and Smith 1985; Robinson et al. 1985a). These effects may result from ischemia-induced increases in extracellular potassium, which in turn may enhance cellular permeabilities to calcium (Robinson et al. 1985b). Furthermore, changes in cytosolic pH and a dysfunction of hydrogen ion handling mechanisms were observed in neuronal cells exposed *in vitro* to cyanide (Maduh et al. 1990b).

In rat neonatal cerebellar granule cells in culture, cyanide increases both reactive oxygen species (RS) and nitric oxide (NO) (Gunasekar et al. 1996). Blockade of glutamate receptors with MK801 markedly reduced both ROS and NO and significantly protected the cells from cyanide damage. Thus, cyanide releases glutamate (Pate1 et al. 1993) which activates NMDA type glutamate receptors which in turn results in increased levels of ROS and NO. It was suggested that NO and ROS react to form a cytotoxic peroxynitrite anion which mediates neurotoxic effects of cyanide.

Recent studies have shown that cyanide releases catecholamines from rat pheochromocytoma cells and brain slices (Kanthasamy et al. 1991b), from isolated bovine adrenal glands (Borowitz et al. 1988), and from the adrenals of mice following subcutaneous injection of high doses of potassium cyanide (Kanthasamy et al. 1991b). Thus, it was proposed that the cardiac and peripheral autonomic responses to cyanide are partially mediated by an elevation of plasma catecholamines (Kanthasamy et al. 1991b).

Reproductive Effects. No studies were located regarding reproductive effects in humans after any route of exposure. Increased resorptions following oral exposure of rats to cyanogenic glycosides in a cassava diet (Singh 1981) and increased gonadal weight in male rats exposed to copper cyanide (Gerhart 1987a) or potassium silver cyanide (Gerhart 1987b) for 90 days were noted. A reduction in the spermatogenic cycle, testicular germ cell sloughing and degeneration, and occasional abnormal cells were noted in dogs fed rice with sodium cyanide added and in dogs fed a cassava diet (Kamalu 1993). A number of reproductive effects were observed following exposure of rats and mice to sodium cyanide in the drinking water for 13 weeks (NTP 1993). In male rats, decreases in the left caudal epididymal weight

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left epididymis weight, left testis weight, spermatid heads, and spermatid counts were noted. In female rats, significantly more time was spent in proestrus and diestrus stages, and less time was spent in estrus and metes&us stages, while in male mice, a significant decrease in the left epididymal and caudal epididymal weights was noted, but no changes in sperm motility or spermatid head density were observed. This study was used as the basis for the oral intermediate MRL. In contrast, no reproductive effects were reported in hamsters exposed to cassava during gestation (Frakes et al. 1986a). Thus, it is possible that exposure to cyanide could lead to reproductive effects in humans.

Developmental Effects. No studies were located regarding developmental effects in humans after any route of exposure and in animals after inhalation and dermal exposure. However, studies in rats (Singh 1981) and hamsters (Frakes et al. 1986a) fed a cassava diet suggested that cyanide may have teratogenic and fetotoxic effects at maternally toxic doses, but Singh (1981) indicated that the results should be interpreted with caution due to the preliminary nature of the report and also indicated that the effects could have been due to the low protein content of the cassava diet. In contrast, Frakes et al. (1986a) clearly showed that the cyanogenic glycosides in the cassava diet or intubation of the principal cyanogenic glycoside (linamarin) (Frakes et al. 1985) were responsible for the adverse developmental effects, since a group of animals fed a diet that resembled cassava in nutritional value, but lacked the cyanogenic glycosides, had only reduced body weight and did not exhibit increased runting or decreased ossification. Similarly, in hamsters, oral doses of D,L-amygdalin also produced teratogenic effects (Willhite 1982), but only at doses that also produced maternal signs of systemic cyanide poisoning. Furthermore, subcutaneous infusions of sodium cyanide to pregnant hamsters increased the incidences of neural tube defects in the offspring (Doherty et al. 1982). In contrast, no teratogenic effects were reported in rats (Tewe and Maner 1981a) or in pigs (Tewe and Maner 1981b) exposed to cassava alone or supplemented with potassium cyanide. Decreased growth was noted in weanling rats of cyanide exposed dams in a two-generation exposure study (Tewe and Maner 1981a). In contrast to oral exposure, no teratogenic effects were observed in hamsters that received d, 1 -amygdalin intravenously (Willhite 1982). The teratogenic effects observed after oral amygdalin and linamarin exposure were due to cyanide releasec by bacterial beta glucosidase in the gastrointestinal tract (Frakes et al. 1985, 1986b; Willhite 1982). The possibility that chronic cyanide consumption, as in cyanogenic plant foods, could cause developmental effects in humans cannot be ruled out.

Genotoxic Effects. *In vitro* genotoxicity studies are summarized in Table 2-4. Cyanide in the form of potassium cyanide tested negative in *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98, TAlOO (De Flora 1981), TA97, and TA102 (De Flora et al. 1984). A positive mutagenic response was

Table 2-4. Genotoxicity of Cyanide *In Vitro*

Species (test system)	End point	Results With activation	Without activation	Reference	Form
Prokaryotic organisms:					
Salmonella typhimurium TA82, TA102	Reverse mutation	–	Not tested	De Flora et al. 1984	KCN
S. typhimurium TA98, TA100, TA1535, TA1537, TA1538	Reverse mutation	–	–	De Flora 1981	KCN
S. typhimurium TA98 TA100	Reverse mutation	– (+)	– +	Kushi et al. 1983	HCN
Escherichia coli WP67, CM871, WP2	DNA repair test	–	–	De Flora et al. 1984	KCN
S. tymphimurium TA97, TA98, TA 100, TA 1535	Reverse mutation	–	–	NTP 1993	NaCN
Eukaryotic organisms: HeLa cells	DNA synthesis inhibition	–	–	Painter and Howard 1982	KCN

DNA = deoxyribonucleic acid; HCN = hydrogen cyanide; KCN = potassium cyanide; NaCN = Sodium cyanide; – = negative result; + = positive result; (+) = weakly positive result

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reported for hydrogen cyanide in strain TA100without metabolic activation (Kushi et al. 1983). Adding S-9 mix to the culture decreased the induction of reverse mutations by cyanide to 40% of the nonactivated reaction. Negative results were also obtained in the DNA repair test in *Escherichia coli* WP67, CM871, and WP2 with potassium cyanide (De Flora et al. 1984). Cyanide in the form of sodium cyanide tested negative in *S. typhimurium* strains TA97, TA98, TA100, and TA 1.535, with and without metabolic activation (NTP 1993).

Only one *in viva* study was located. No testicular DNA-synthesis inhibition was detected in mice after a single oral dose of 1 mg/kg cyanide as potassium cyanide (Friedman and Staub 1976). The results indicate that cyanide, especially in a form of salts, is not mutagenic.

Cancer. No studies were located regarding carcinogenic effects of cyanide exposure in humans or animals following any route of exposure. Therefore, no hypothesis can be made as to whether or not an increased risk of cancer can be expected in populations exposed to cyanide.

2.6 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAXNRC 1989).

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s), or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to cyanide are discussed in Section 2.6.1.

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Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are often not substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by cyanide are discussed in Section 2.6.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic, or a preexisting disease that results in an increase in absorbed dose, biologically effective dose, or target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.8, Populations That Are Unusually Susceptible.

2.6.1 Biomarkers Used to Identify or Quantify Exposure to Cyanide

Methods are available to measure levels of cyanide and its metabolite, thiocyanate, in blood and urine. High blood cyanide levels of 250-300 μg/l00 mL were reported in cases of death from cyanide poisoning (Vogel et al. 198 1). The relationship between increased exposure and increased urine levels of thiocyanate was demonstrated in workers exposed occupationally to 6.4-10.3 ppm cyanide in air (El Ghawabi et al. 1975). In another study, blood cyanide concentrations varied from 0.54 to 28.36 μg/l00 mL in workers exposed to ≈ 0.2-0.8 ppm cyanide in air and from 0.0 to 14.0 μg/l00 mL in control workers (Chandra et al. 1988). Correspondingly, blood thiocyanate concentrations were 0.05-2.80 mg/100 mL in exposed workers and 0.02-0.88 mg/100 mL in control workers, respectively. Data obtained from the controls indicate that cyanide can be detected in populations exposed to low cyanide levels in the environment. Cyanide-containing food, metabolism of certain drugs, and combustion of nitrogenous polymers are among several sources of cyanide exposure. Furthermore, industrially polluted air, soil, and water may contribute to higher environmental cyanide levels.

Several studies showed increased cyanide and thiocyanate levels in body fluids of smokers. The difference between smokers and nonsmokers can be quite distinct (Maliszewski and Bass 1955). Mean thiocyanate levels in smokers and nonsmokers, respectively, were found to be 7.1 and 2.0 μg/mL in plasma, 75.7 and 20.3 μg/mL in saliva, and 12.3 and 2.1 μg/mL in urine. A more recent study also

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reported on mean thiocyanate levels in smokers and nonsmokers, respectively (Jarvis 1989). Levels reported were 7.1 and 2.9 μg/mL in plasma, 142 and 76 μg/mL in saliva, and 9.0 and 5.8 μg/mL in urine. Another study found a correlation between the number of cigarettes smoked per day and the thiocyanate levels in plasma and in saliva (Yamanaka et al. 1991). Based on changes in salivary thiocyanate in 6 smokers who stopped smoking, this study estimated the half-life of salivary thiocyanate to be 9.5 days. In addition, infants living in homes with family members who smoked heavily were found to have significantly higher serum thiocyanate levels than those infants who were not exposed to cigarette smoke in the home (Chen et al. 1990). It is unclear whether passive smoking (exposure of a nonsmoker to air contaminated with tobacco smoke) is a factor in elevated fetal serum thiocyanate levels. In one study, fetal thiocyanate levels were increased in association with passive smoking in the home (Bottoms et al. 1982), while another study did not report an association (Hauth et al. 1984).

Whether it is more appropriate to use whole blood or plasma for measuring cyanide concentrations has been the subject of several reports. Cyanide plasma levels are usually about one-third to one-half, depending on the species, those found in whole blood (Ballantyne 1983a). However, they can more closely reflect the actual tissue dose. Furthermore, cyanide was found to attach more readily to plasma albumin than to hemoglobin (McMillan and Svoboda 1982). It was suggested that hemoglobin in erythrocytes binds cyanide molecules, but does not play any role in their metabolism. Some authors argue cyanide in red blood cells may be biologically active (Way 1984). In addition, it is known that cyanide rapidly leaves serum and plasma, especially in the first 20 minutes. It may be appropriate to measure cyanide in both whole blood and plasma. Whole blood samples can be stored at 4 °C for several weeks with little change in cyanide content.

In cyanide-poisoning cases, any blood levels of cyanide >0.2 μ/L indicate a toxic situation (Berlin 1977). However, because cyanide binds tightly to cytochrome c oxidase, serious effects can also occur at lower levels; therefore, the clinical condition of the patient should be considered when determining proper therapy.

An almond-like smell in the breath of a poisoned patient can warn a physician that the individual may be suffering from cyanide poisoning. Approximately 60-70% of the population can detect the bitter almond odor of hydrogen cyanide. The odor threshold for those sensitive to the odor is estimated to be l-5 ppm in the air. However, even at high toxic concentrations up to 20% of all individuals are genetically unable to smell hydrogen cyanide (Snodgrass 1996). Some effects of cyanide that can also be used to monitor exposure are discussed in Section 2.5.2.

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2.6.2 Biomarkers Used to Characterize Effects Caused by Cyanide

Cyanide can inhibit enzymatic activity by binding to some metallic moieties in metalloenzymes (Ardelt et al. 1989; Way 1984) and cytochrome c oxidase is especially sensitive to cyanide inhibition. Consequent to the inhibition, theoretically, oxygen cannot be used and histotoxic anoxia occurs. Death is caused by respiratory failure. Dyspnea, palpitations, hypotension, convulsions, and vomiting are among the first effects of acute cyanide poisoning (see Section 2.2). Ingestion of amounts 2 50-100 mg sodium or potassium cyanide may be followed by almost instantaneous collapse and cessation of respiration (Hartung 1982). Data summarized by Hartung (1982) indicate that exposure to a concentration in air of 270 ppm causes immediate death; concentrations of 181 ppm and 135 ppm are fatal after 10 and 20 minutes of exposure, respectively; concentrations between 45 and 55 ppm can be tolerated for 30-60 minutes with immediate or late effects; and 18-36 ppm may produce slight symptoms after several hours of exposure. Following chronic exposure, cyanide has been associated with the development of tropical neuropathy, tobacco amblyopia, and Leber's hereditary optic atrophy (Wilson 1965). Chronic exposure to cyanide arising from consumption of cyanogenic plant foods has also been connected with the occurrence of endemic goiter (Delange and Ermans 1971).

For more information on biomarkers for renal and hepatic effects of chemicals see ATSDR/CDC Subcommittee Report on Biological Indicators of Organ Damage (1990) and for information on biomarkers for neurological effects see OTA (1990).

2.7 INTERACTIONS WITH OTHER CHEMICALS

A number of compounds act in synergy with cyanide to produce toxic effects. In smoke, hydrogen cyanide may interact with other toxicants (Birky and Clarke 198 1). High blood cyanide levels were found in fire victims; however, the carboxyhemoglobin levels were also high. Thus, it is difficult to assess the significance of hydrogen cyanide in the toxicity. The authors suggested that sublethal concentrations of hydrogen cyanide may interact with other toxicants to potentiate the toxic and lethal effects. They also speculated that cyanide could increase incapacitation of the victim, preventing escape, so that the victim could be exposed to high levels of carbon monoxide.

In an investigation to examine toxicological interactions of the primary fire gases, the additive, synergistic, or antagonistic effects of combinations of hydrogen cyanide with carbon monoxide or with carbon dioxide on the 30-minute LC_{50} value for hydrogen cyanide alone were determined in rats (Levin et

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al. 1987). Co-exposure of rats to hydrogen cyanide (LC_{50} = 110 ppm) and carbon monoxide (LC_{50} = 4,600 ppm) resulted in lethal effects of these two gases that were additive. In contrast, co-exposure to hydrogen cyanide and 5% carbon dioxide (not lethal by itself) resulted in an increase in lethality of hydrogen cyanide, reflected as a decrease of the hydrogen cyanide LC_{50} value to 75 ppm. Dodds et al. (1992) also investigated the interaction between cyanide and carbon monoxide in rats, and found an additive effect on certain parameters, including lactate elevation and neurologic index.

Addition of sodium cyanide (5 mmol) and tributyltin (10 μmol) to human erythrocyte suspensions resulted in a synergistic increase in tributyltin-induced hemolysis (Gray et al. 1986). Mechanisms are not clear, but may involve elevated pH of high sodium cyanide concentrations.

Synergism has also been observed between cyanide and ascorbic acid. Guinea pigs exhibited increased toxic effects when treated with ascorbic acid prior to oral administration of potassium cyanide (Basu 1983). When guinea pigs were treated solely with potassium cyanide, 38% exhibited slight tremors, whereas 100% of those treated with ascorbic acid and potassium cyanide exhibited severe tremors, ataxia, muscle twitches, paralysis, and convulsions. It has been suggested that this synergistic effect results from the ability of ascorbic acid to compete with cyanide for cysteine, thus diminishing the detoxication of cyanide.

Antidotes for cyanide poisoning have been intensively studied and reviewed (Way 1984). Cyanide antagonists can be classified into two general groups: those that act as sulfane sulfur donors for rhodanese catalyzed cyanide detoxification and those that induce chemical binding of cyanide. Sulfur donors include sodium thiosulfate, polythionates, and thiosulfates. Sodium thiosulfate has been successfully used as an antidote against cyanide poisoning in humans for decades (Way 1984). A pharmacokinetic study in dogs demonstrated that intravenous administration of thiosulfate increased the detoxification rate of intravenously given cyanide to thiocyanate over 30 times (Sylvester et al. 1983). Pretreatment with thiosulfate decreased the biological half-life of cyanide from ≈ 39 minutes to ≈ 15 minutes and also decreased the volume of distribution of cyanide from 498 mL/kg to 204 mL/kg. Thiosulfate pretreatment had prophylactic effects in guinea pigs exposed to cyanide by intravenous infusion (Mengel et al. 1989). The protection lasted for several hours depending on the dose of thiosulfate administered.

Antagonists that induce the chemical binding of cyanide to sites other than cytochrome c oxidase include sodium nitrite, amyl nitrite, and hydroxylamine. These compounds generate methemoglobin, which competes with cytochrome c oxidase for cyanide to form cyanmethemoglobin (Way 1984). Sodium nitrite

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has been effectively used in the therapy of cyanide intoxication in humans especially in combination with sodium thiosulfate (Smith 1996; Way 1984). Studies in mice demonstrated that intraperitoneal pretreatment with sodium nitrite more than doubled the LD_{50} value of intraperitoneally administered sodium cyanide from 3.18 to 7.95 mg CN^-/kg (Kruszyna et al. 1982). Peak methemoglobinemia was 35% at 40 minutes. Other methemoglobin generating agents seemed to be less effective. 4-Dimethylaminopropiophenol enhanced the LD_{50} value to 6.36 mg CN^-/kg and hydroxylamine to 4.66 mg CN^-/kg with peak methemoglobinemia being 40% and 36%, respectively at 7 minutes. The data suggested that sodium nitrite, a slow methemoglobin former, gave prolonged protection against cyanide, while animals treated with fast methemoglobin formers died later on, probably due to the cyanide release from the cyanmethemoglobin pool. An improvement of cyanide-altered cerebral blood flow was observed in dogs treated with sodium nitrite or 4-dimethylaminophenol following intravenous injection of hydrogen cyanide (Klimmek et al. 1983).

Cobalt-containing compounds may also function as binders by forming a stable complex with cyanide. A dramatic antagonism of the lethal effects of potassium cyanide was reported when cobaltous chloride was administered to mice along with sodium thiosulfate (Isom and Way 1974a). The authors suggested that this synergistic antidotal effect of cobaltous chloride may be associated with the physiological disposition of the cobaltous ion and its ability to chelate both thiocyanate and cyanide ions. This ability is also utilized when (dicobalt ethylenediamine tetra-acetate acid (CO_2EDTA) is used as a cyanide antidote. An improvement of cerebral aerobic metabolism and blood flow was observed in dogs treated with 10 mg/kg Co_2EDTA intravenously following intravenous application of 1.6 mg CN^-/kg as potassium cyanide (Klimmek et al. 1983). A lower molecular weight porphyrin cobalt compound than hydroxocobalamin (CoTPPS) was used as an antidote to the lethal effects of cyanide (McGuinn et al. 1994). The interaction with hydroxocobalamin (see Section 2.3.3) was also proposed as a mechanism for cyanide detoxification in cases of acute poisoning. It was demonstrated that intravenous administration of hydroxocobalamin (50-250 mg/kg) prior to or after intraperitoneal injection of potassium cyanide prevented lethality and decreased cyanide-induced toxic effects in mice (Mushett et al. 1952).

Pretreatment of rats with chlorpromazine (10 mg/kg intramuscularly) and sodium thiosulfate (1,000 mg/kg intraperitoneally) greatly decreased or abolished the increase in plasma creatine kinase observed in rats exposed to hydrogen cyanide at 200 ppm for 12.5 minutes (O'Flaherty and Thomas 1982). In an in vitro study, chlorpromazine and 4,4'-diisothiocyano-2,2'-stilbene disulfonic acid reduced cyanide-induced contractions in vascular smooth muscle (Robinson et al. 1985a). It was suggested that chlorpromazine

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prevents cyanide-induced calcium influx and reduces peroxidation of membrane lipids (Maduh et al. 1988).

The ability of cyanide to combine with carbonyl groups of some intermediary metabolites (e.g., sodium pyruvate, a-ketoglutarate) to form cyanohydrin has been used for antidotal purposes. Pretreatment of mice with 1 g/kg sodium pyruvate intraperitoneally prior to subcutaneous injection of potassium cyanide caused an increase in the LD_{50} values from 3.1 to 5 mg CN^-/kg (Schwartz et al. 1979). Sodium pyruvate also prevented the development of convulsions in cyanide-exposed mice. Similarly, intraperitoneal pretreatment of mice with 2 g/kg α-ketoglutarate before the intraperitoneal injection of potassium cyanide increased the LD_{50} value from 2.68 to 13.32 mg CN^-/kg (Moore et al. 1986). It was further demonstrated that both sodium pyruvate and a-ketoglutarate enhanced the antidotal effects of other cyanide antagonists (e.g., sodium thiosulfate, sodium nitrite) (Moore et al. 1986; Schwartz et al. 1979).

A striking protection against cyanide can be elicited by an new conceptual approach, employing carrier erythrocytes containing highly purified rhodanese. Several studies have shown that resealed erythrocytes containing rhodanese and sodium thiosulfate rapidly metabolize cyanide to the less toxic thiocyanate (Cannon et al. 1994; Petrikovic et al. 1995). Maduh and Baskin (1994) showed that rhodenase may be regulated by protein phosphorylation and treatments that alter the phosphorylation state of rhodenase may affect cyanide detoxification via formation of thiocyanate.

Several papers discuss the effects of oxygen alone or with other compounds on cyanide toxicity. Oxygen alone results in minimal antagonism in mice injected with potassium cyanide and only slightly enhances the antagonistic effects of sodium nitrite (Sheehy and Way 1968). The antidotal effect of sodium thiosulfate alone or in combination with sodium nitrite, was enhanced by oxygen.

Oxygen-treated mice did not show behavioral signs of cyanide intoxication below doses of 2.4 mg CN^-/kg as potassium cyanide; whereas air-treated animals showed effects such as gasping, irregular breathing, and convulsions at levels as low as 1.2 mg CN^-/kg as potassium cyanide (Isom et al. 1982). When mice were pretreated with sodium nitrite and sodium thiosulfate and either air or oxygen, the dose of potassium cyanide needed to cause a 59% inhibition of brain cytochrome c oxidase more than doubled in mice in an oxygen atmosphere; all points on the oxygen curve differed significantly from the air-treatment curve.

A striking enhancement of the oxidation of glucose to carbon dioxide was observed when oxygen, sodium nitrite, and sodium thiosulfate were given to mice dosed at 18 mg CN^-/kg as potassium cyanide; no

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enhancement was noticed at 4 or 6 mg CN⁻/kg as potassium cyanide (Isom and Way 1974b). These studies indicate that oxygen can be used in supporting classical cyanide antagonists in the therapy of cyanide poisoning, but even hyperbaric oxygen alone had no effect on cyanide poisoning in mice (Way et al. 1972). The mechanism of the action is not known, since cyanide inhibits the cellular utilization of oxygen through inhibiting cytochrome c oxidase and, theoretically, the administration of oxygen should have no effect or useful purpose (Smith 1996).

2.8 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to cyanide than will most persons exposed to the same level of cyanide in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters may result in reduced detoxification or excretion of cyanide, or compromised function of target organs affected by cyanide. Populations who are at greater risk due to their unusually high exposure to cyanide are discussed in Section 5.6, Populations With Potentially High Exposure.

Persons with a metabolic disturbance in the conversion of cyanide to thiocyanate may be at greater risk. A defect in the rhodanese system and vitamin B_{12} deficiency have been associated with tobacco amblyopia and Leber's hereditary optic atrophy in persons exposed to cyanide in tobacco smoke (Wilson 1983).

A number of dietary deficiencies may increase the risk of deleterious cyanide effects. Iodine deficiency is involved in the etiology of such thyroid disorders as goiter and cretinism. These disorders may be exacerbated by excess exposure to cyanide (Delange and Ermans 1971; Ermans et al. 1972). Protein deficiencies and vitamin B_{12}, riboflavin and other vitamins and elemental deficiencies may subject people in the tropics who eat cassava to increased risks of tropical neuropathies (Makene and Wilson 1972; Osuntokun 1972; Osuntokun et al. 1969). However, a recent study reported that scopoletin, a potent hypotensive and spasmolytic agent found in cassava roots, may be the etiological agent in the tropical neuropathies observed among cassava eaters, rather than cyanide (Obidoa and Obasi 1991). Furthermore, children and women seem to be more susceptible to the endemic spastic paraparesis in the cassava-consumption regions (Rosling 1987). Studies that have uncovered more severe effects in nutritionally deprived animals (Kreutler et al. 1978; Rutkowski et al. 1985) provide support to the observations in humans.

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In areas where cassava is a staple food, congenital hypothyroidism is present in 15% of newborns (Ermans et al. 1980), indicating that fetuses may be at a higher risk. Animal studies provide further evidence that fetuses may be at a higher risk than the general population. Developmental toxicity has been observed in rodents following inhalation, oral, and parenteral exposure to cyanide-containing compounds (Doherty et al. 1982, 1983; Frakes et al. 1985, 1986a; Singh 1981; Willhite 1982), but not free cyanide.

One group of people who may be at greater risk are those who are exposed to cyanide but are unable to smell the chemical (Kirk and Stenhouse 1953; Snodgrass 1996). Patients with motor neuron disease (amyotrophic lateral sclerosis) possess a disorder in cyanide detoxification that may result in their higher susceptibility to cyanide (Kato et al. 1985).

2.9 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to cyanide. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to cyanide. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following texts provide specific information about treatment following exposures to cyanide:

- Ellenhorn, MJ and Barceloux, DG. 1988. *Medical Toxicology, Diagnosis and Treatment of Human Poisoning.* Elsevier Publishing. New York, New York;
- Gosselin RE, Smith RP and Hodge, HC. 1984. Clinical Toxicology of Commercial Products. 5th edition. 111-123-130. Williams and Wilkins, Baltimore, Maryland; and
- LaDou, JY. 1990. *Occupational Medicine.* Appleton & Lange. Norwalk, Connecticut and San Mateo, California.

2.9.1 Reducing Peak Absorption Following Exposure

Human exposure to cyanide may occur by inhalation, ingestion, or by dermal contact, but the general population is more likely to be exposed by inhaling air or ingesting food or water contaminated with cyanide. General recommendations for reducing absorption of cyanide from inhalation and dermal exposure include removing the exposed individual from the contaminated area and removing the contaminated clothing (Ellenhorn and Barceloux 1988; Goldfrank et al. 1990; Stutz and Janusz 1988). If the eyes and skin are exposed, they should be flushed with water. However, in order not to become

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secondary victims, rescuers may enter potentially contaminated areas only with self-contained breathing apparatus and protective clothing. Speed is essential during a rescue operation.

In order to reduce absorption of ingested cyanide, gastric lavage may be performed immediately after ingestion. Individuals exposed by any route are commonly administered 100% oxygen and assisted ventilation, including endotracheal intubation, as needed. Hyperbaric oxygen has been advocated when patients do no respond to standard therapy (Litovitz et al. 1983); however, studies in laboratory animals suggest hyperbaric oxygen is no more effective than normobaric oxygen (Way 1984). An antidotal combination of inhaled amyl nitrate and intravenous sodium nitrite and sodium thiosulfate are often indicated. Monitoring for metabolic acidosis, cardiac dysrhythmias, and possible pulmonary edema is suggested.

2.9.2 Reducing Body Burden

The primary target for cyanide toxicity is the central nervous system following both acute and chronic exposure. Exposure to high doses of cyanide can rapidly lead to death (see Section 2.2). Cyanide is not stored in the organism and one available study indicates that >50% of the received dose can be eliminated within 24 hours (Okoh 1983). However, because of the rapid toxic action of cyanide, development of methods that would enhance metabolism and elimination of cyanide is warranted.

Cyanide is metabolized in the body by two metabolic pathways that have been identified (Ansell and Lewis 1970). The first and major metabolic pathway involves the transfer of sulfane sulfurs from a donor to cyanide to yield thiocyanate (see Section 2.3). The reaction employs the enzyme rhodanese as a catalyst. Thiocyanate is a fairly stable compound and is excreted predominately in urine. Serum proteins (especially albumin) are a major internal pool of sulfane sulfurs. Their protective role against cyanide toxicity was confirmed in tests with laboratory animals (Rutkowski et al. 1985; Tewe and Maner 1980, 1982). Cyanide antagonists help convert cyanide to thiocyanate. Sodium thiosulfate is commonly used in cases of cyanide poisoning, (Bonsall 1984; Mengel et al. 1989; Schubert and Brill 1968; Sylvester et al. 1983). An increase in antidotal effect was noted when rhodanese was combined with thiosulfate (Frankenberg 1980). Similarly, other sulfane sulfur donors have protective effects against cyanide toxicity.

The second and minor metabolic pathway consists of the reaction of cyanide with cystine to yield cysteine and β-thiocyanoalanine (Wood and Cooley 1955). The latter is then converted to 2-imino-

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4-thiazolidinecarboxylic acid and excreted in urine. Cystine has not been used for the purpose of mitigation of cyanide effects because its contribution to detoxification via this pathway is minor.

2.9.3 Interfering with the Mechanism of Action for Toxic Effects

The mechanism of acute cyanide toxicity is well understood (see Section 2.4). Cyanide inhibits the activity of some enzymes by binding to their metallic moiety. By blocking the action of cytochrome c oxidase, histotoxic hypoxia/anoxia develops rapidly in exposed organisms (Smith 1996). The ability of cyanide to bind to some metallic ions is utilized with antidotes that cause methemoglobinemia in exposed organisms. Cyanide binds to the ferric ion of methemoglobin to form inactive cyanmethemoglobin (see Section 2.6). Antidotes utilized for this purpose either clinically or experimentally include amyl nitrite, sodium nitrite, hydroxylamine, p-aminopropiophenone, 4-dimethylaminophenol, and primaquine (Bhattacharya 1995; Bright and Marrs 1987; Kruszyna et al. 1982; Scharf et al. 1992; Schubert and Brill 1968). The disadvantage of these antidotes is that the methemoglobinemia further aggravates the depletion of tissues from oxygen; therefore, antidote-induced methemoglobin levels need to be closely followed in clinical practice.

Cyanide's binding to metallic ions is also employed in a reaction with cobalt-containing compounds that yields cyanocobalamin (see Section 2.6). Cobalt compounds generally are not used because of their toxicity; however, Co,EDTA (Klimmek et al. 1983) and hydroxocobalamin (Benabid et al. 1987; Mengel et al. 1989; Mushett et al. 1952) have been used as antidotes both in clinical and laboratory trials. Cardiac toxicity from Co_2EDTA use under clinical conditions has raised caution in its clinical use, as the cardiac toxicity of cobalt is well known (Way 1984). Both of these antidotes have the advantage of not inducing methemoglobinemia. A recent study (McGuinn et al. 1994) used a lower molecular weight cobalt porphyrin compound (CoTPPS) as an antidote to the lethal effects of cyanide. This compound was found to have a high affinity for cyanide due to its low molecular weight, and it allows administration in threefold molar excess of binding sites over a lethal dose of cyanide. Similarly, cyanide forms stable complexes with selenite (Palmer and Olson 1979). It is possible that further research may develop other metal-containing compounds usable as cyanide antidotes.

In an effort to find additional antidotes that would not produce methemoglobinemia, compounds such as sodium pyruvate, dihydroxyacetone, α-ketoglutarate (Niknahad and O'Brien 1996), oxaloacetate, pyridoxal 5'-phosphate, chlorpromazine, and naloxone (Way 1984) have been introduced (see Section 2.7). Interactions of cyanide with carbonyl groups of these compounds lead to formation of inert cyanohydrin

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intermediates (Keniston et al. 1987; Moore et al. 1986; Schwartz et al. 1979; Yamamoto 1989). Niknahad et al. (1994) demonstrated that dihydroxyacetone and glyceraldehyde are much more effective than pyruvate and a-ketoglutarate as cyanide antagonists, and Hume et al. (1995) showed that α-ketoglutaric acid and sodium thiosulfate are synergistic in their antidotal effects against hydrogen cyanide and sodium cyanide.

Pharmacological approaches to finding antidotes for cyanide are also under investigation. Maduh et al. (1995) examined the effects of a protein kinase C inhibitor, 1-5-(isoquinolinesulfonyl)-2 methylpiperazine (H-7), on cellular energy depletion caused by sodium cyanide. They reported that H-7 partially prevented cellular energy depletion and increased the number of surviving cells.

In addition, other chemicals such as a-adrenergic blocking agents like chlorpromazine (O'Flaherty and Thomas 1982; Way and Burrows 1976) or oxygen (Burrows et al. 1973; Sheehy and Way 1968) may be used to enhance the protective action of other antidotes. However, the mechanism of their action is not well understood. Further research for a potent and safe antidote, particularly among smoke inhalation victims who have carbon monoxide poisoning, to mitigate cyanide toxicity is desirable.

It must be stressed that the therapeutic value of the antidotes mentioned above is heavily dependent on the time lapse between intoxication and their use, since the usual course of inorganic cyanide poisoning is acute and proceeds at very high speeds.

Sun et al. (1995) reported that the nitric oxide generator, isosorbide dinitrate, is an effective cyanide antidote in mice. They showed that the mechanism does not involve methemoglobin formation and suggested that nitric oxide might antagonize the respiratory depressant effects of cyanide. Other more efficient nitric oxide generators may be very useful cyanide antidotes.

2.10 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of cyanide is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of cyanide.

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The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce or eliminate the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

2.10.1 Existing Information on Health Effects of Cyanide

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to cyanide are summarized in Figure 2-6. The purpose of this figure is to illustrate the existing information concerning the health effects of cyanide. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need." A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

In the section that follows, data needs are identified for cyanide forms for which toxicity data were available and were, therefore, summarized in Section 2.2. These forms include primarily sodium cyanide, potassium cyanide, and hydrogen cyanide. As seen from Figure 2-6, information is available regarding death, systemic effects of acute exposure, and neurological effects in humans after inhalation, oral, and dermal exposure to cyanide. In addition, information is available regarding chronic systemic effects in humans after inhalation and oral exposure.

Data regarding death, systemic effects of acute exposure, and neurological effects were obtained for animals following inhalation, oral, and dermal exposure to cyanide. Furthermore, information was obtained regarding systemic effects after intermediate-duration inhalation and oral exposure, and chronic oral exposure. In addition, information exists regarding developmental and reproductive effects after oral exposure of animals to cyanide.

Figure 2-6. Existing Information on Health Effects of Cyanide

Human

Animal

●   Existing Studies
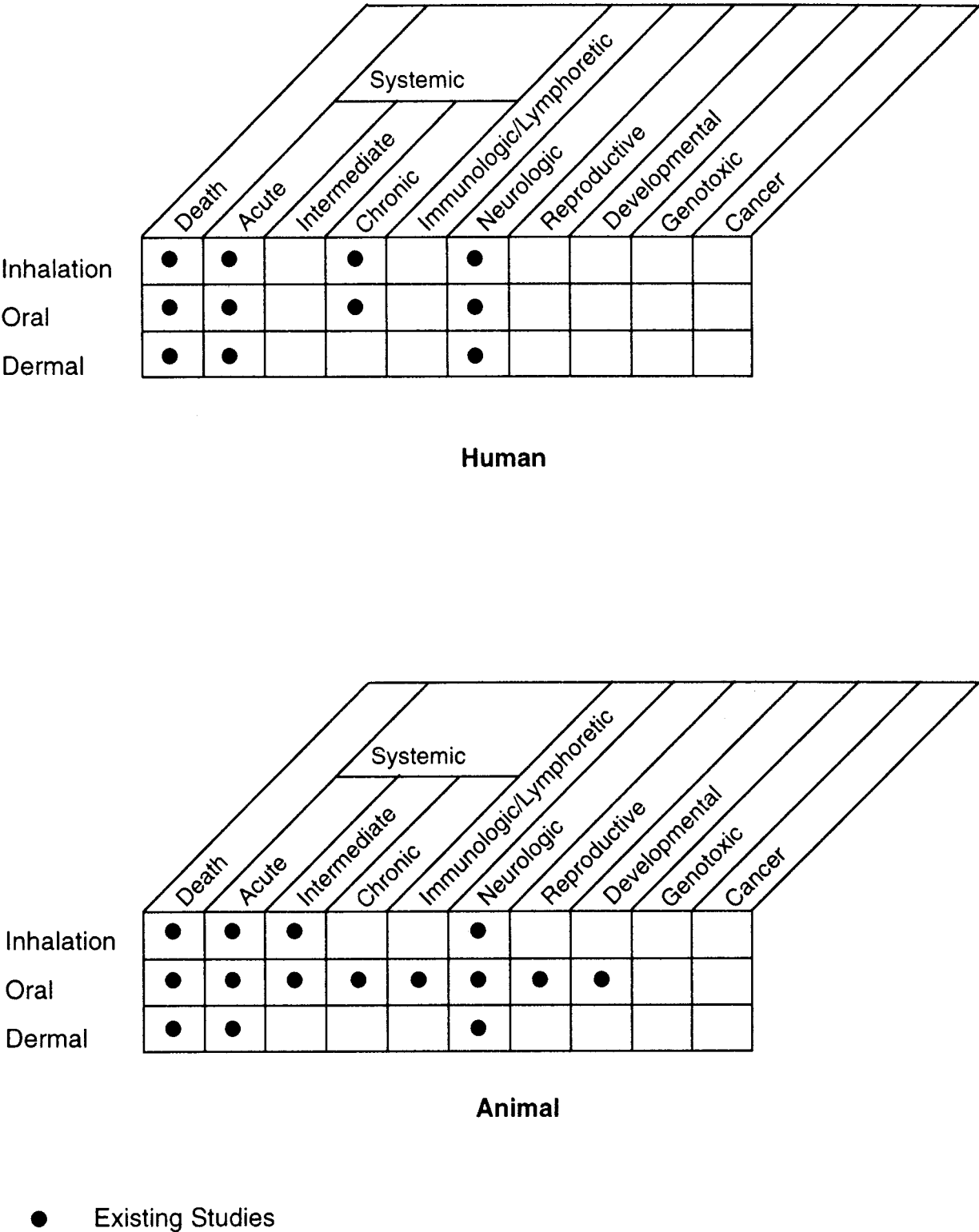
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2.10.2 Identification of Data Needs

Acute-Duration Exposure. The target organs of acute cyanide exposure are the central nervous system, respiratory system, and cardiovascular system. Exposure to high levels of cyanide leads rapidly to death. Lethality data are available in humans for acute inhalation (Dudley et al. 1942; Singh et al. 1989), oral (Gettler and Baine 1938), and dermal (Rieders 1971) exposures to hydrogen cyanide; however, specific exposure levels are often not available. Lethality studies were performed in several animal species, and LC_{50} and LD_{50} values were derived for inhalation (hydrogen cyanide and cyanogen) (Ballantyne 1983a), oral (potassium cyanide and sodium cyanide) (Ballantyne 1983a, 1988), and dermal (hydrogen cyanide, potassium cyanide, and sodium cyanide) (Ballantyne 1983a, 1988) exposures. The most common systemic effects observed were dyspnea and palpitations. The effects were seen in humans regardless of route of cyanide exposure. Since most of the animal studies reported lethality as an end point, information regarding acute systemic effects in animals is limited and no suitable NOAEL or LOAEL values are available to serve as the basis for MRLs. Additional acute studies by all routes using several dose levels and examining comprehensive end points would help to determine thresholds for known target organs and for any new target organs that might be identified. The information would be useful to populations living near hazardous waste sites that can be exposed to cyanide in contaminated water or soil for a short time.

Intermediate-Duration Exposure. No intermediate-duration studies were located regarding cyanide effects in humans. A few inhalation (Valade 1952) and oral (Gerhart 1987a, 1987b; Jackson 1988; Kamalu 1993; NTP 1993; Philbrick et al. 1979; Tewe and Maner 1981 b) studies in animals indicated that the target organs of intermediate-duration exposure to cyanide toxicity are the central nervous system (potassium cyanide and hydrogen cyanide) and the reproductive system (sodium cyanide). In addition, dermal, hematological, hepatic, and renal effects may be caused by oral exposure. No intermediateduration dermal studies were available. It is known, however, that cyanides can rapidly penetrate the skin and similar toxic effects are presumed. No intermediate-duration inhalation MRL could be derived because of the lack of data. An intermediate oral MRL of 0.05 mg/kg/day was derived from a study showing reproductive effects in rats exposed to 12.5 mg/kg/day cyanide in the drinking water for 13 weeks, as sodium cyanide (NTP 1993). This study is further described in the section on Reproductive Toxicity below. Additional intermediate-duration inhalation studies using several dose levels would be useful to determine threshold levels.

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Chronic-Duration Exposure and Cancer. Some reports of occupationally exposed workers indicated that low concentrations of hydrogen cyanide may have caused neurological, respiratory, and cardiovascular effects (Blanc et al. 1985; Chandra et al. 1980, 1988; El Ghawabi et al. 1975; Kumar et al. 1992). The route of exposure was predominantly inhalation, although dermal exposure can also occur in the work place. The studies, however, lacked either information about exposure levels or used small cohorts of workers. Studies in populations that used cassava roots as a main source of their diet described the neurological effects of cyanide consumption (Osuntokun 1972, 1980). However, these effects may be due to a recently identified substance, scopeletin, rather than due to cyanide (Obidoa and Obasi 1991). For chronic exposure in animals, only one oral study in rats (hydrogen cyanide) was located (Howard and Hanzal 1955). However, the reliability of this study is low because of the unstable cyanide levels in their feed throughout the experiment due to evaporation of cyanide. Furthermore, no effects were found in the study besides nondose-related changes in weight gain in female rats, but not in male rats. No chronic studies in animals were located for the inhalation and dermal routes. Therefore, data are not sufficient to derive MRL values for chronic exposure. Additional chronic-duration studies in animals would be helpful to determine thresholds for target organs.

No studies were located regarding carcinogenicity of cyanide in humans or animals. The results of the chronic bioassays suggested above may contribute some new insights.

Genotoxicity. No human data are available on the genotoxicity of cyanide. In *vitro* studies with cyanide in the form of potassium cyanide did not show any mutagenic activity in *S. typhimurium* or *E. coli* (De Flora 1981; De Flora et al. 1984), and cyanide in the form of sodium cyanide tested negative in *SulmoneZla* strains TA97, TA98, TA100, and TA1535, with and without metabolic activation (NTP 1993). One study in *S. typhimurium* suggested that hydrogen cyanide may be mutagenic (Kushi et al. 1983); an increase in the induction of reverse mutations was noted without metabolic activation. No genotoxicity was found in one *in vivo* study with potassium cyanide in mice (Friedman and Staub 1976). In summary, no human studies are available and *in vitro* studies have shown primarily negative results. There are no structural reasons to suggest that cyanide may be genotoxic. Thus, it does not appear that further genotoxicity studies are needed at this time.

Reproductive Toxicity. No data were located regarding reproductive effects of cyanide in humans. One animal study reported increased resorptions in rats following oral exposure to a cassava diet (Singh 1981). Because some human populations use cassava roots as the main source of their diet, further information regarding this observation would be useful for these populations, but this is probably not a

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concern for people living in the United States. Increased gonadal weight was found in male rats in 90-day oral studies of copper cyanide and potassium silver cyanide (Gerhart 1987a, 1987b). A number of reproductive effects, including decreases in left cauda epididymal weight, left testis weight, spermatid heads, and spermatid counts were noted in rats exposed to sodium cyanide in the drinking water for 13 weeks (NTP 1993). This study was used as the basis for the intermediate oral MRL. Thus, it appears that only limited value would be associated with further reproductive studies at this time.

Developmental Toxicity. No studies were located regarding developmental effects in humans exposed to cyanide by any route. Developmental studies in animals were performed only following oral exposure and contradicting results were obtained. Teratogenic effects of cyanide exposure were observed in rats and hamsters fed a cassava diet (Frakes et al. 1986a; Singh 1981), while no effects were found in rats and pigs fed cassava diets alone or supplemented with potassium cyanide in other studies (Tewe and Maner 1981 a, 1981b). Furthermore, growth retardation was the only effect in weanling rats in the second generation of a two-generation oral exposure study with potassium cyanide. More data regarding developmental toxicity in experimental animals would be useful to identify the possible risk for humans.

Immunotoxicity. No data were located regarding immunological effects in humans or animals after inhalation, oral, or dermal exposure to cyanide. A battery of immune function tests has not been performed in humans or animals but would be useful to clarify whether cyanide is an immunotoxin.

Neurotoxicity. The central nervous system is an important target for cyanide toxicity in humans and animals following exposure by all three routes. Acute inhalation exposure to high levels of cyanide, regardless of the form, leads quickly to death that is preceded by dyspnea, convulsions, and central nervous system depression (Bonsall 1984; Chen and Rose 1952; Peden et al. 1986; Potter 1950; Singh et al. 1989). Neurological and behavioral effects were observed in humans after chronic inhalation exposure to hydrogen cyanide in the workplace (Blanc et al. 1985; Chandra et al. 1988; El Ghawabi et al. 1975). Oral exposure to cyanide led to the development of severe peripheral neuropathies, and hearing and visual problems in those who used cassava as a staple in the diet (Osuntokun 1980). However, these effects may be due to a recently identified substance, scopeletin, rather than due to cyanide (Obidoa and Obasi 1991). Experimental studies in animals exposed to hydrogen cyanide or cyanide compounds by the inhalation (Purser et al. 1984; Valade 1952), oral (Philbrick et al. 1979), or dermal routes (Ballantyne 1983b), have found neurological effects similar to those seen in humans. Behavioral changes were reported in pigs after oral exposure to cyanide; however, the animals were experimentally compromised as they were starved (Jackson 1988). Additional studies for neurological effects for all routes and durations would be useful

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for determining the NOAEL values for this most sensitive end point. Of particular value would be studies that correlate morphological changes, such as demyelination, with changes in higher functions, such as learning and memory.

Epidemiological and Human Dosimetry Studies. Human exposure to low levels of cyanide is quite common. Cigarette and fire smoke contain cyanide (Fiksel et al. 1981); it is used as a postharvest fumigant (Jenks 1979) and can even be detected in drinking water supplies (Fiksel et al. 1981). Furthermore, workers are exposed to cyanide in several industries (Blanc et al. 1985). Although several studies reported neurological and thyroid effects in workers chronically exposed occupationally, dose relationships of these effects are not known, and the effects may have been confounded by simultaneous exposure to other chemicals. Similarly, exact correlations between environmental exposures and cyanide levels in blood or urine were not established. Therefore, occupational and environmental studies that would provide data on exposure levels and concentrations found in body fluids would be useful. These studies might be useful for establishing cause/effect relationships that might lead to future monitoring of populations exposed to low levels of cyanide from dietary sources or contaminated waste sites. Furthermore, studies regarding the health status, including urinary thiocyanate as a biomarker, of such populations would be informative. Studies examining exposure to cyanide via cassava consumption would not be useful, since cassava is not normally consumed in the United States; additionally researchers have recently noted that another substance rather than cyanide may be the neurotoxic agent in cassava (Obidoa and Obasi 1991).

Biomarkers of Exposure and Effect.

Exposure. Concentrations, of cyanide and its metabolite thiocyanate can be measured in the blood, urine, and tissues. Since certain amounts of cyanide can always be found in the human tissues, urine, and expired air, only exposure to high doses can be detected by this way. Cyanide is metabolized in the body to thiocyanate in a reaction that is catalyzed by an enzyme rhodanese and mercaptopyruvate sulfur transferase (Ansell and Lewis 1970).

Effect. No biomarkers were identified that are useful for characterizing effects induced by exposure to cyanide. The target organs of cyanide toxicity are the central nervous system and the cardiovascular system. However, exposure to other chemicals may have similar effects. More studies to identify subtle biochemical changes to serve as biomarkers of effects of cyanide exposure would be useful.

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Absorption, Distribution, Metabolism, and Excretion. Hydrogen cyanide, sodium cyanide, and potassium cyanide are readily absorbed following inhalation, oral, and dermal exposures (Ballantyne 1983a). Inhalation exposure provides the most rapid route of entry. Cyanide is distributed throughout the body and detoxified by a mitochondrial enzyme, rhodanese (Ansell and Lewis 1970). Other detoxification pathways include spontaneous reaction with cystine and the reaction with hydroxocobalamin. The severity and rapidity of the onset of effects depend on the route, dose, duration of exposure, and the cyanide compound administered. Once cyanides have been absorbed, excretion is similar in humans and animals. Cyanide metabolites are excreted primarily in urine, and small amounts of hydrogen cyanide are eliminated through the lungs (Farooqui and Ahmed 1982; Okoh 1983). Additional quantitative data on the toxicokinetics of cyanide would be useful, because there are few studies available that quantitate absorption and distribution. No data were found that dealt with saturation kinetics in cyanide metabolism, since cyanide is fatal long before saturation is reached.

Comparative Toxicokinetics. Several studies on cyanide lethality and toxicity indicate that the central nervous system, the reproductive system, and the thyroid gland are target organs in both humans and animals. Toxicokinetic studies have not been performed in humans; however, data regarding cyanide distribution have been obtained during autopsies in several lethal cases of poisoning following inhalation or oral exposure to hydrogen cyanide, sodium cyanide, or potassium cyanide (Finck 1969; Gettler and Baine 1938). Most of the toxicokinetic studies in animals were published between 1935 and 1965. As a result, much of the information is descriptive rather than quantitative, and the quantitative data presented were generated with inaccurate analytical equipment and methodologies. However, more recent studies in rats with hydrogen cyanide, sodium cyanide, and potassium cyanide indicate a pattern of distribution that is similar to that in humans (Ballantyne 1983a, 1983b; Yamamoto et al. 1982). Furthermore, a study regarding transocular exposure showed that tissue concentrations of cyanide in rabbits varied depending on the cyanide compound used (Ballantyne 1983a, 1983b). Detailed pharmacokinetic studies on cyanide and thiosulfate have been conducted in dogs (Sylvester et al. 1983). Additional toxicokinetic data in several species would be needed to identify the best model for assessing human risk.

Methods for Reducing Toxic Effects. The mechanism by which cyanide enters the blood stream in humans is not known; but due to the relatively small size of the molecule, it is possible that cyanide simply follows a concentration gradient. Some of the mechanisms of toxic action of cyanide are known: the compound inhibits the activity of various enzymes by binding to their metallic moiety. Cyanide antagonists, such as sodium thiosulfate, have been used as antidotes to cyanide poisoning by aiding in the conversion of cyanide to thiocyanate (Bonsall 1984; Mengel et al. 1989; Schubert and Brill 1968;

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Sylvester et al. 1983). Other antidotes such as amyl nitrite, sodium nitrite, hydroxylamine, p-aminopropiophenone, 4-dimethylaminophenol, and primaquine work by binding to metallic ions and causing methemoglobinemia (Bright and Mans 1987; Kruszyna et al. 1982; Sharf et al. 1992; Schubert and Brill 1968). Additional research has been carried out on antidotes that would not produce methemoglobinemia (Klimmek et al. 1983; Niknahad and O'Brien 1996), and recent studies have examined the synergistic effects of several antidotes (Hume et al. 1995; Niknahad et al. 1994), as well as pharmacological approaches to finding antidotes for cyanide (Maduh et al. 1995).

2.10.3 Ongoing Studies

A number of ongoing studies concerning health effects and mechanisms of action associated with cyanide have been identified in the Federal Research in Progress (FEDRIP) database. A study at Purdue University is investigating the mechanisms of action of cyanide-induced neurotoxicity. A study at the University of Nevada is investigating the potential health effects from acute and intermediate exposure periods to sublethal levels of cyanide in drinking water. Symbiotech, Inc., is developing a pretreatment against hydrogen cyanide and cyanogen chloride when used as chemical warfare agents. Two additional ongoing studies were identified: the Department of Veterans Affairs is sponsoring a study testing the effect of two regimens of thiosulfate and nitroprusside on serum cyanide levels on post-operative patients receiving high levels of nitroprusside; a University of Alabama study is investigating the role of thiocyanate in human health (FEDRIP 1996).

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

Information regarding the chemical identity of cyanide is located in Table 3-l. Hydrogen cyanide is a toxic gas which enters the environment from both natural processes and human industrial activities. It may exist in polymeric forms. The cyanide compounds in which cyanide can be obtained as CN⁻ are classified as simple and complex cyanides. Some simple cyanides are soluble in water (sodium cyanide, NaCN; potassium cyanide, KCN; calcium cyanide, $Ca(CN)_2$), while others are sparingly soluble or almost insoluble (copper (I) cyanide, CuCN). Cyanogen chloride (CNC_l) is a highly toxic gas that is soluble in water. At alkaline pH, CNC1 hydrolyzes to CNO⁻ which has only limited toxicity. Alkaline chlorination of water containing cyanide produces cyanogen chloride. Thiocyanate (SCN⁻) is an oxidation product of cyanide, produced in the presence of sulfur.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of cyanide is located in Table 3-2. Cyanides form strong complexes with many metals, particularly those of the transition series. One example of such complexation is the reaction of cyanide with iron in the formation of ferrocyanide and ferricyanide complexes. Solutions of ferrocyanides and ferricyanides can form hydrogen cyanide and cyanide ions when exposed to sunlight or ultraviolet radiation. Cyanogenic glycosides are cyanide compounds produced naturally in many plants. These glycosides produce hydrogen cyanide when hydrolyzed (Towill et al. 1978).

Hydrogen cyanide has a pK_a of 9.2 (Smith and Martell 1989); therefore, solutions of cyanide compounds in water (such as from sodium cyanide and potassium cyanide) can form hydrogen cyanide at acid and neutral pHs. Alkaline solutions with pH >12 are practical for preventing significant outgassing of hydrogen cyanide.

Hydrogen cyanide is a fire hazard and may be explosive when an excess of a strong acid is added to confined hydrogen cyanide. Solutions of some cyanide compounds are not stable and may decompose upon exposure to air or light.

Table 3-1. Chemical Identity of Cyanide and Compounds[a]

Characteristic	Hydrogen cyanide	Sodium cyanide	Potassium cyanide	Calcium cyanide
Synonym(s)	Formonitrile; hydrocyanic acid; prussic acid	Cyanide of sodium; hydrocyanic acid; sodium salt	Cyanide of potassium; hydrocyanic acid, potassium salt	Calcid; calcyan; cyanide of calcium
Registered trade name(s)	Cyclone B; Cyclon[b]	Cyanogran[c]	Carswell No. 688A	Caswell No. 142 Cyanogas[c]
Chemical formula	HCN	NaCN	KCN	$Ca(CN)_2$
Chemical structure	$H^+C \equiv N^-$	$Na^+C \equiv N^-$	$K^+C \equiv N^-$	$^-N \equiv CCa^{+2}C \equiv N^-$
Identification numbers:				
CAS registry	74–90–8	143–33–9	151–50–8	592–01–8
NIOSH RTECS	MW6825000	VZ7530000	TS8750000	EW0700000
EPA hazardous waste	P063, D003	P106; D003	P098; D003	P021; D003
OHM/TADS	7216749	7216892	7216862	7216626
DOT/UN/NA/IMCO shipping	UN1051; IMO 6.1 UN1614; NA 1051	UN1689; IMO 6.1	UN1680; IMO 6.1	UN1575; IMO 6.1
HSDB	165	734	1245	242
NCI	No data	No data	No data	No data

Table 3-1. Chemical Identity of Cyanide and Compounds[a] (continued)

Characteristic	Copper(I) cyanide	Potassium silver cyanide	Cyanogen	Cyanogen chloride
Synonym(s)	Cuprous cyanide[c]; cupricin[c]	Potassium argento-cyanide; potassium dicyanoargentate	Carbon nitride; dicyanogen; ethanedinitrile	Chlorine cyanide; chlorocyan
Registered trade name(s)	AI3–28745	No data	No data	Caswell No. 267
Chemical formula	CuCN	$KAg(CN)_2$	$(CN)_2$	CNCl
Chemical structure	$Cu^+C \equiv N^-$	$K^+[Ag(CN)_2]^-$	$N \equiv C - C \equiv N$	$Cl - C \equiv N$
Identification numbers:				
CAS registry	544–92–3	506–61–6	460–19–5	506–77–4
NIOSH RTECS	GL7150000	TT5775000	GT1925000	GT2275000
EPA hazardous waste	P029; D003	P099; D003; D011	P031; D003	P033; D003
OHM/TADS	No data	No data	7216656	7216658
DOT/UN/NA/IMCO shipping	UN1587; IMO 6.1	No data	UN1026; IMO 2.3	UN1589; IMO 2.3
HSDB	1438	6053	2130	917
NCI	No data	No data	No data	No data

Table 3-1. Chemical Identity of Cyanide and Compounds[a] (continued)

Characteristic	Ammonium thiocyanate
Synonym(s)	Thiocyanic acid, ammonium salt; ammonium rhodanide; ammonium sulfocyanate[c]
Registered trade name(s)	Trans-Aid[b]
Chemical formula	$NH_4^+S - C \equiv N^-$
Chemical structure	NH_4SCN
Identification numbers:	
CAS registry	1762-95-4
NIOSH RTECS	XK7875000
EPA hazardous waste	No data
OHM/TADS	721218
DOT/UN/NA/IMCO shipping	NA9092
HSDB	701
NCI	No data

[a]All data are from HSDB 1996 unless otherwise noted.
[b]Farm Chemicals Handbook 1983
[c]Merck 1989

CAS = Chemical Abstracts Service; DOT/UN/NA/IMO = Dept. of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

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Table 3-2. Physical and Chemical Properties of Cyanide and Compounds

Property	Hydrogen cyanide	Sodium cyanide
Molecular weight	27.03[a]	49.01[a]
Color	Colorless[h]	White[h]; colorless[a]
Physical state	Gas or liquid[h]	Solid[h]
Melting point, °C	−13.4[h]	563.7[a]
Boiling point, °C	25.70[d]	1496[a]
Density, g/cm^3	0.6884 (liquid at 20 °C)[d];	1.60 (for cubic form)[d]
Odor	Faint bitter almond odor[c]	Odorless when dry, emits slight odor of HCN in damp air[h]
Odor threshold:		
Water	0.17 ppm (w/v)[b]	No data
Air	0.58 ppm (v/v)[b]; 0.8-4.4 ppm[g]	No data
Solubility:		
Water	Miscible[a]	48 g/100 mL at 10 °C[d]
Organic solvent(s)	Soluble in ethanol, ether[a]	Slightly soluble in ethanol[a] and formamide[d]
Partition coefficients:		
Log K_{ow}	0.66[e]; 1.07 (calc.)[l]	0.44[e]
Log K_{oc}	No data	No data
Vapor pressure, mm Hg	630 (at 20 °C)[g]	0.76 at 800 °C[d]
Henry's law constant	5.1×10^{-2} atm–m^3/mol[f]	No data
Autoignition temperature	538[d]	No data
Flashpoint, °C	−17.8 (closed cup)[d]	No data
Flammability limits	5.6–40%[n]	Not combustible[n]
Conversion factors:		
mg/m^3 to ppm in air, 20 °C	1 mg/m^3 = 0.890 ppm	NA[i]
ppm to mg/L in water	ppm (w/v) = mg/L = μg/mL	ppm (w/v) = mg/L = μg/mL
ppm to mg/kg in soluble samples	ppm (w/w) = mg/kg = μg/g	ppm (w/w) = mg/kg = μg/g
Explosive limits	Upper, 40%; lower, 5.6%[g]	No data

3. CHEMICAL AND PHYSICAL INFORMATION

Table 3-2. Physical and Chemical Properties of Cyanide
and Compounds (continued)

Property	Potassium cyanide	Calcium cyanide
Molecular weight	65.12[a]	92.12[a]
Color	White[h]; colorless[a]	White[a]
Physical state	Solid[h]	Solid[a]
Melting point, °C	634.5[a]	Decomposes at >350 °C[a]
Boiling point, °C	No data	No data
Density, g/cm^3	1.553 (for cubic form)[d]	1.8–1.9 (commercial product)[d]
Odor	Faint bitter almond odor[h]	Faint bitter almond odor[h]
Odor threshold:		
Water	No data	No data
Air	No data	No data
Solubility:		
Water	71.6 g/100 mL at 25 °C[d]	Soluble in water with gradual liberation of HCN[h]
Organic solvent(s)	Slightly soluble in ethanol[d] and methanol[h]	
Partition coefficients:		
Log K_{ow}	No data	No data
Log K_{oc}	3.0 (calc.)[m]	No data
Vapor pressure, mm Hg	No data	No data
Henry's law constant	No data	No data
Autoignition temperature	No data	No data
Flashpoint	No data	No data
Flammability limits	Not combustible[n]	Not combustible[n]
Conversion factors:		
mg/m^3 to ppm in air, 20 °C	NA[i]	NA[i]
ppm to mg/L in water	ppm (w/v) = mg/L = µg/mL	ppm (w/v) = mg/L = µg/mL
ppm to mg/kg in soluble samples	ppm (w/w) = mg/kg = µg/g	
Explosive limits	No data	No data

Table 3-2. Physical and Chemical Properties of Cyanide and Compounds (continued)

Property	Potassium silver cyanide	Cyanogen
Molecular weight	199.01[h]	52.04[a]
Color	White[h]	Colorless[a]
Physical state	Solid[h]	Gas[a]
Melting point, °C	No data	–27.9[a]
Boiling point, °C	No data	–20.7[a]
Density, g/cm^3	2.36[a]	0.9577 at –21.17 °C[a]
Odor	No data	Almond–like odor[h]
Odor threshold:		
Water	No data	No data
Air	No data	230 ppm; irritating at 15 ppm[g]
Solubility:		
Water	Soluble[h]	450 cc/100 cc (20 °C)[a]
Organic solvent(s)	Slightly soluble in ethanol[a]	Soluble in ethanol and ethyl ether[a]
Partition coefficients:		
Log K_{ow}	No data	No data
Log K_{oc}	No data	No data
Vapor pressure, mm Hg	No data	3,800 at 20 °C[j]
Henry's law constant	No data	No data
Autoignition temperature	No data	No data
Flashpoint	No data	No data
Flammability limits	No data	6.6 – 32% in air[n]
Conversion factors:		
mg/m^3 to ppm in air, 20 °C	NA[i]	1 mg/m^3 = 0.462 ppm
ppm to mg/L in water	ppm (w/v) = mg/L = μg/mL	ppm (w/v) = mg/L = μg/mL
ppm to mg/kg in soluble samples	ppm (w/w) = mg/kg = μg/g	ppm (w/w) = mg/kg = μg/g
Explosive limits	No data	No data

3. CHEMICAL AND PHYSICAL INFORMATION

Table 3-2. Physical and Chemical Properties of Cyanide and Compounds (continued)

Property	Cyanogen chloride	Copper(I) cyanide
Molecular weight	61.47[a]	89.56[a]
Color	Colorless[c]	White to cream-colored[h]
Physical state	Gas[c]	Solid[a]
Melting point, °C	–6[a]	473 (in N_2)[a]
Boiling point, °C	13.8[h];12.7[a]	Decomposes[a]
Density, g/cm^3	1.186[h]	2.92[a]
Odor	Highly irritating[h]	No data
Odor threshold:		
Water	No data	No data
Air	1 ppm[g]	No data
Solubility:		
Water	Soluble[h]	Insoluble[a]
Organic solvent(s)	Soluble in ethanol and ethyl ether[h]	Insoluble in alcohol[g]
Partition coefficients:		
Log K_{ow}	No data	No data
Log K_{oc}	No data	No data
Vapor pressure, mm Hg	760 at 13.8 °C	No data
Henry's law constant	No data	No data
Autoignition temperature	No data	No data
Flashpoint	No data	No data
Flammability limits	Not combustible[g]	Does not readily ignite[g]
Conversion factors:		
mg/m^3 to ppm in air, 20 °C	1 mg/m^3 = 2.5 ppm	NA[i]
ppm to mg/L in water	ppm (w/v) = mg/L = µg/mL	ppm (w/v) = mg/L = µg/mL
ppm to mg/kg in soluble samples	ppm (w/w) = mg/kg = µg/g	ppm (w/w) = mg/kg = µg/g
Explosive limits	No data	No data

3. CHEMICAL AND PHYSICAL INFORMATION

Table 3-2. Physical and Chemical Properties of Cyanide and Compounds (continued)

Property	Ammonium thiocyanate
Molecular weight	76.12[a]
Color	Colorless[a]
Physical state	Solid[a]
Melting point, °C	149.6[a]
Boiling point, °C	170 decomposes[a]
Density, g/cm^3	1.305[a]
Odor	Odorless[h]
Odor threshold:	
Water	No data
Air	No data
Solubility:	
Water	128 g/100 cc at 0 °C; v soluble in hot water[a]
Organic solvent(s)	v soluble in ethanol; soluble in acetone and methanol; insoluble in ethyl acetate and chloroform[h]
Partition coefficients:	
Log K_{ow}	No data
Log K_{oc}	No data
Vapor pressure, mm Hg	No data
Henry's law constant	No data
Autoignition temperature	No data
Flashpoint	No data
Flammability limits	May be combustible[g]
Conversion factors:	
mg/m^3 to ppm in air, 20 °C	NA[i]
ppm to mg/L in water	ppm (w/v) = mg/L = µg/mL
ppm to mg/kg in soluble samples	ppm (w/w) = mg/kg = µg/g
Explosive limits	No data

[a]Lide 1993
[b]Amoore and Hautala 1983
[c]Hawley 1981
[d]Jenks 1979
[e]EPA 1984a
[f]Yoo et al. 1986; value at 25 °C and saturation pressure
[g]HSDB 1994
[h]Merck 1989

[i]Since these compounds do not exist in the atmosphere in the vapor phase, their concentrations are always expressed in weight by volume unit (e.g., mg/m^3).
[j]Towill et al. 1978
[k]Sax 1984
[l]Verschueren 1983
[m]Kenaga 1980
[n]NFPA 1994

EPA = Environmental Protection Agency; HCN = hydrogen cyanide; HSDB = Hazardous Substances Data Bank; NA = not applicable

4. PRODUCTION, lMPORT/EXPORT, USE, AND DISPOSAL

4.1 PRODUCTION

The demand for hydrogen cyanide in the United States during 1992 was 1.2 billion pounds; this demand is projected to grow 3-4% per year up to 1.46 billion pounds in 1997. The demand for hydrogen cyanide increased by 3-4% per year during the period of 1983-92 (CMR 1993). Major producers of hydrogen cyanide are American Cyanamid Co. (Fortier, Louisiana); BP Chemicals (Green Lake, Texas and Lima, Ohio); Ciba-Geigy Corp. (St. Gabriel, Louisiana); Cyanco Co. (Winnemucca, Nevada); Cytec Industries (Avondale, Louisiana); Degussa Corp. (Theodora, Alabama); Dow Chemical (Freeport, Texas); DuPont (Memphis, Tennessee; Beaumont, Texas; Orange, Texas; and Victoria, Texas); FMC Corporation (Green River, Wyoming); Monsanto (Alvin, Texas and Chocolate Bayou, Texas); Rh&e-Poulenc Ag Company (Institute, West Virginia); Rhom and Haas Texas Inc. (Deer Park, Texas); and Sterling Chemicals, Inc. (Texas City, Texas) (CMR 1993; SRI 1995). The combined annual production capacity of these plants is approximately 1.7 billion pounds (CMR 1993; SRI 1995). Producers of hydrogen cyanide in the United States having maximum on-site amounts greater than 100,000 pounds are: American Cyanamid Co. (Louisiana), BP Chemicals (Texas and Ohio), Ciba-Geigy Corp. (Louisiana), Degussa Corp. (Alabama), Du Pont Chemical Company (two Texas sites), and Monsanto (Texas) (TR193 1995).

As of January 1994, the following companies produced other cyanide compounds in the United States (HSDB 1996; SRI 1994, 1995):

ammonium thiocyanate:	Witco Corporation, Taft, Louisiana;
	Akzo America, Inc., Janesville, Wisconsin; and
	The Proctor and Gamble Company, Phillipsburg, New Jersey;
cyanogen:	Matheson Gas Products, Inc., Gloucester, Massachusetts;
potassium cyanide:	Du Pont Chemical Company, Memphis, Tennessee; and
	Hampshire Chemical Corporation, Nashua, New Hampshire; and
potassium silver cyanide:	Engelhard Corporation, Union, New Jersey; and American
	Chemical & Refining Company, Waterbury, Connecticut.

Facilities producing sodium cyanide and their annual capacity (in millions of pounds) include: Cyanco Co., Winnemucca, Nevada (28); Degussa Corporation, Theodore, Alabama (60); Du Pont Chemical Company, Memphis, Tennessee (250) and Texas City, Texas (100); and FMC Corporation, Green River, Wyoming (60) (SRI 1995).

4. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

Facilities in each state that manufactured or processed hydrogen cyanide in 1992, the range of the maximum amounts stored on site, and the types of production or use activities (e.g., production for sale or on-site use in processing) are shown in Table 4-l (TR193 1995). The information in Table 4-l is derived from the Toxics Release Inventory (TRI). The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. No information is available in the TRI database for other cyanide and thiocyanate compounds in this profile because these compounds are not included under SARA, Title III and, therefore, are not among the chemicals that facilities are required to report (EPA 1993g).

There are two common methods of manufacturing hydrogen cyanide. The first consists of the formation of hydrogen cyanide as a by-product during the synthesis of acrylonitrile from the reaction of propylene and ammonia with air. The second method involves direct synthesis by the reaction of methane and ammonia with air over platinum catalysts (CMR 1993; Curry 1992; Homan 1987). Other methods of production include the dehydration of formamide, and reaction of sodium carbonate with coke-oven gas (Curry 1992; Sittig 1980). The formamide method of production has now been replaced by direct synthesis from methane and ammonia (Homan 1987). Of the total production capacity, direct synthesis accounts for 77% of the hydrogen cyanide produced; by-product of acrylonitrile production accounts for the remaining 23% (CMR 1993; SRI 1995). The methods of commercial production of potassium and sodium cyanide include reacting potassium or sodium carbonate with carbon and ammonia, and reacting hydrogen cyanide with potassium or sodium hydroxide (Curry 1992; HSDB 1996). Sodium cyanide can also be prepared by heating sodium amide with carbon or by melting sodium chloride and calcium cyanamide together in an electric furriace (Hartung 1982). Potassium silver cyanide is manufactured by adding silver chloride to a solution of pot&ssium cyanide (Sax and Lewis 1987). Calcium cyanide is manufactured by heating calcium cyanamide with a source of carbon in electric furnaces at temperatures greater than 1,000 °C (Curry 1992; Homan 1987). It may also be produced by neutralization of lime with hydrogen cyanide (Homan 1987).

Cyanogen is usually prepared by adding an aqueous solution of sodium or potassium cyanide to an aqueous solution of copper sulfate(II) or chloride (Homan 1987; Windholz 1983). It may also be produced by heating mercury cyanide, or by heating hydrogen cyanide in the presence of a catalyst (Homan 1987). Cyanogen chloride is produced by the action of chlorine on hydrogen cyanide or by the action of chlorine on moist sodium cyanide suspended in carbon tetrachloride and kept cooled to -3 °C (Homan 1987; Windholz 1983). Ammonium thiocyanate is produced by boiling an aqueous solution of

Table 4-1. Facilities That Manufacture or Process Hydrogen Cyanide

Facility	Location[a]	Range of maximum amounts on site in pounds	Activities and uses
DEGUSSA CORP.	THEODORE, AL	100,000-999,999	Produce; For on-site use/processing; For sale/distribution; As a reactant
VEBA CORP.	THEODORE, AL	100,000-999,999	As a reactant
ULTRAMAR CORP.	WILMINGTON, CA	0-99	Produce; As an impurity
MITSUBISHI RAYON CO. LTD.	SACRAMENTO, CA	100-999	Produce; As a by-product
PMC INC.	CHICAGO, IL	0-99	Produce; As a by-product
NA	ASHLAND, KY	0-99	Produce; As an impurity
NA	ASHLAND, KY	0-99	Produce; As a by-product; As an impurity
CABOT CORP.	VILLE PLATTE, LA	100-999	Produce; As a by-product
CIBA-GEIGY CORP.	ST. GABRIEL, LA	1,000,000-9,999,999	Produce; For on-site use/processing; As a reactant
DOW CHEMICAL CO.	PLAQUEMINE, LA	1,000-9,999	Produce; As a by-product
NA	WESTWEGO, LA	100,000-999,999	Produce; For on-site use/processing; As a by-product; As a reactant
CABOT CORP.	FRANKLIN, LA	100-999	Produce; As a by-product
KOCH IND. INC.	ROSEMOUNT, MN	100-999	Produce; As a by-product; As an impurity
HAMPSHIRE HOLDINGS CORP.	NH	1,000,000-9,999,999	As a reactant
ARCADIAN CORP.	LIMA, OH	1,000,000-9,999,999	Produce; For sale/distribution; As a by-product
HAMPSHIRE CHEMICAL CORP.	LIMA, OH	1,000-9,999	As a reactant
LONZA INC.	WILLIAMSPORT, PA	100,000-999,999	As a reactant
AMOCO CHEMICAL CO.	PIEDMONT, SC	0-99	Produce; As a by-product
ALBEMARLE CORP.	ORANGEBURG, SC	10,000-99,999	As a reactant
BASF CORP.	ROCK HILL, SC	0-99	Produce; As a by-product
AKZO NOBEL NV	ROCKWOOD, TN	0-99	Produce; As a by-product
E. I. DU PONT DE NEMOURS & CO.	MEMPHIS, TN	1,000,000-9,999,999	Produce; For on-site use/processing; For sale/distribution; As a by-product; As a reactant
ICI AMERICAS INC.	MEMPHIS, TN	1,000-9,999	As a reactant
MONSANTO CO.	ALVIN, TX	100,000-999,999	Produce; Import; For on-site use/processing; As a by-product; As a reactant
DOW CHEMICAL USA	FREEPORT, TX	0-99	Produce; For on-site use/processing; As an impurity; As a reactant

Table 4-1. Facilities That Manufacture or Process Hydrogen Cyanide (continued)

Facility	Location[a]	Range of maximum amounts on site in pounds	Activities and uses
BP AMERICA	PORT LAVACA, TX	100,000-999,999	Produce; For on-site use/processing; As a by-product; As an impurity; As a reactant
NA	TEXAS CITY, TX	10,000-99,999	Produce; For on-site use/processing; As a by-product; As a reactant
CABOT CORP.	PAMPA, TX	0-99	Produce
ROHM & HAAS CO.	DEER PARK, TX	10,000-99,999	Produce; For on-site use/processing; As a reactant
NA	DEER PARK, TX	100,000-999,999	As a reactant
W. R. GRACE & CO.-CONN.	DEER PARK, TX	0-99	As a reactant
ISK ENTERPRISES CORP.	HOUSTON, TX	100-999	Produce; As a by-product
E. I. DU PONT DE NEMOURS & CO.	BEAUMONT, TX	10,000-99,999	Produce; For on-site use/processing; For sale/distribution; As a by-product; As a reactant
ICI ACRYLICS INC.	NEDERLAND, TX	10,000-99,999	As a reactant
E. I. DU PONT DE NEMOURS & CO.	ORANGE, TX	100,000-999,999	Produce; For on-site use/processing; For sale/distribution; As a reactant
E. I. DU PONT DE NEMOURS & CO.	VICTORIA, TX	No Data	Produce; For on-site use/processing; As a reactant
HERCULES INC.	MAGNA, UT	0-99	Produce; As a by-product
MURPHY OIL USA INC.	SUPERIOR, WI	0-99	Produce; As a by-product
CABOT CORP.	WAVERLY, WV	0-99	Produce; As a by-product
FMC CORP.	GREEN RIVER, WY	0-99	Produce; For on-site use/processing; As a reactant

Source: TRI93 1995

[a] Post office state abbreviations used

NA = not available

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ammonium cyanide with sulfur or polysulfides or by reaction of ammonia and carbon disulfide (Homan 1987; Sax and Lewis 1987).

4.2 IMPORT/EXPORT

The imports and exports of hydrogen cyanide through principal U.S. customs districts are negligible (CMR 1993). Recent import and export data for some of the cyanide compounds included in this profile are summarized in Table 4-2 (USDOC 1994, 1995). As shown in Table 4-2, over the period January 1990 through December 1993, import volumes for thiocyanates, cyanates, and fulminates increased, whereas import volumes of calcium cyanide, cyanides and cyanide oxides of sodium, other cyanides and cyanide oxides, and non-aromatic thiocyanates used for pesticides decreased markedly. Import volumes for potassium cyanide also decreased during the period January 1990 through December 1992, but it was the only compound listed that increased steadily over the next 2 years. Italy, Germany, and Great Britain were the primary exporters of these cyanide chemicals to the United States (USDOC 1994). The most recent import data that could be found for copper (I) cyanide indicate that 0.52 and 0.26 million pounds of this compound were imported into the United States in 1984 and 1986, respectively (HSDB 1996). Recent import data could not be found in the available literature for potassium silver cyanide, cyanogen, or cyanogen chloride.

Export volumes of cyanide compounds (foreign and domestic volumes combined) shown in Table 4-2 fluctuated widely over the period January 1989 and April 1994. No obvious trends were evident except for potassium cyanide, where export volumes decreased from 3.13 million pounds in 1989 to 0.46 million pounds in 1994. Export data could not be found in the available literature for calcium cyanide, potassium silver cyanide, cyanogen, or cyanogen chloride.

4.3 USE

The predominant users of cyanides are the steel, electroplating, mining, and chemical industries. The principal cyanide compounds used in industrial operations are potassium and sodium cyanide and calcium cyanide, particularly in metal leaching operations (Curry 1992; EPA 1992g). Cyanides have well established uses as insecticides and fumigants; in the extraction of gold and silver ores; in metal cleaning; in the manufacture of synthetic fibers, various plastics, dyes, pigments, and nylon; and as reagents in analytical chemistry (EPA 1992g; Towill et al. 1978). Cyanogen has been used as a high-energy fuel in the chemical industry and as a rocket or missile propellant; cyanogen and its halides are used in organic

Table 4-2. Import and Export Volumes of Cyanide Compounds[a]

Compounds	Imports (million pounds)						Exports (million pounds)						
	1990	1991	1992	1993	1994	Total[b]	1989	1990	1991	1992	1993	1994	Total[c]
Potassium cyanide	1.59	1.29	1.29	1.55	1.67	7.39	3.13	1.99[d]	0.21	0.27	0.49	0.46[d]	6.55
Calcium cyanide	12.01	12.30	1.78	ND[e]	ND	26.09[f]	ND	ND	ND	ND	ND	ND	
Cyanides and cyanide oxides of sodium	28.14	28.94	10.10	6.77	5.68	79.63	123.3	142.9	104.6	132.9	136.6	150.2[d]	790.5
Other cyanides and cyanide oxides	0.67	1.49	1.25	1.29	1.21	5.91	1.04	0.94	0.86	0.70	1.50	0.91	5.95
Thiocyanates, cyanates, and fulminates	1.11	1.49	1.85	1.89	1.62	7.96	1.39	0.80	0.72	0.82	0.90	3.07	7.70
Nonaromatic thiocyanates used for pesticides	ND	2.66	2.21	1.30	0.40[g]	6.57	ND	ND	ND	ND	ND	ND	

[a]USDOC (1994, 1995).
[b]Total import volume from January 1990 through December 1994.
[c]Total export volume from January 1989 through December 1994.
[d] Values represent domestic export volumes only.
[e]ND = No data.
[f]Total import volume for 1990 through 1992.
[g]Import volume from January through April 1994

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syntheses, as pesticides and fumigants, and in gold-extraction processes (Towill et al. 1978). When used in pesticidal applications and in accordance with the product label, cyanide compounds are regulated by the EPA under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) (EPA 1992g).

As a commercially available product, hydrogen cyanide is sold as a gas and is also available as a technical grade liquid in concentrations of 5, 10, and 96-99.5%. Almost all grades of hydrogen cyanide contain a stabilizer such as phosphoric acid to prevent decomposition and explosion (Curry 1992). In recent years, the use of hydrogen cyanide in the nylon and methyl methacrylate production processes has produced a strong demand. The use pattern for hydrogen cyanide is the following: adiponitrile (for nylon 6/6), 43%; methyl methacrylate, 32%; sodium cyanide, 10%; cyanuric chloride, 5%; chelating agents, 5%; and miscellaneous uses, including methionine and nitriloacetic acid, 5% (CMR 1993). Miscellaneous applications also include the use of hydrogen cyanide as an insecticide and rodenticide for fumigating enclosed spaces (grain storage, etc.) (Worthing 1987) and its use in the manufacture of ferrocyanides, acrylates, lactic acid, pharmaceutical, and specialty chemicals (Worthing 1987).

Cyanide salts have various uses. The most significant applications of compounds included in this profile are uses in electroplating and metal treatment, as an anti-caking agent in road salts, and in gold and silver extraction from ores. Minor applications include use as insecticides and rodenticides, as chelating agents, and in the manufacture of dyes and pigments (Sax and Lewis 1987; Towill et al. 1978; Worthing 1987). Calcium cyanide is used as a cement stabilizer (Curry 1992; Windholz 1983) and has had limited use in rodent control and as a beehive fumigant (Lowe and Sullivan 1992). Formerly used as a polymerization catalyst and as an antifouling agent in marine paints, copper (I) cyanide continues to be used in plating baths for silver, brass, and copper-tin alloy plating. Many metal polishes contain potassium or sodium cyanide. Potassium cyanide has a primary use in silver plating and is also used as a reagent in analytical chemistry. Potassium and sodium cyanide are used in combination for nitriding steel (HSDB 1996). One method of achieving hardened, weather-resistant metal surfaces uses a process known as cyaniding which involves heating the metal in a liquid solution of sodium cyanide, sodium chloride and sodium carbonate in the presence of atmospheric oxygen (Curry 1992). Fumigation of fruit trees, railway cars, and warehouses, and treatment of rabbit and rat burrows and termite nests are included among the former uses for sodium cyanide (HSDB 1996).

Cyanogen, a colorless gas with an almond-like odor, is used in organic syntheses, as a fumigant, as a fuel gas for welding and cutting heat-resistant metals, and as a rocket and missile propellant with ozone or fluorine (Sax and Lewis 1987; HSDB 1996). Applications of cyanogen chloride include use in chemical

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syntheses, as a military poison gas, as a warning agent in fumigant gases, as a metal cleaner, in ore refining, and in the production of triazine herbicides, optical brighteners, dyestuffs and synthetic rubber (Farm Chemicals Handbook 1994; Hartung 1982; Homan 1987; HSDB 1996; Windholz 1983).

Ammonium thiocyanate is used as an ingredient in antibiotic fermentations, pesticides, liquid rocket propellants, adhesives, and matches; in photographic processes; to improve the strength of silks; in the manufacture of transparent artificial resins; and as a weed killer and defoliant (Sax and Lewis 1987; Windholz 1983).

4.4 DISPOSAL

It has been estimated that 4.7 billion gallons of cyanide-containing wastes and 0.8 billion gallons of reactive wastes containing cyanide compounds were generated in the United States in 1983 (Grosse 1986). Regulations governing the treatment and disposal of cyanide-containing wastes are detailed in Chapter 7. Cyanide is listed among the 65 toxic pollutants regulated by the Effluent Guidelines and Standards given in Title 40, Sections 400-475, of the Code of Federal Regulations. The pretreatment standards established for point source categories such as hydrogen peroxide manufacturing, electroplating, metal finishing, and ferroalloy manufacturing, regulate cyanides as cyanide amenable to chlorination or total cyanide. Under the Resource Conservation and Recovery Act (RCRA), cyanide is listed as a hazardous waste when it is a discarded as a commercial chemical product, off-specification species, container residue, or spill residue (EPA 1980a); a waste from non-specific sources; or a waste from specific sources. Cyanide salts and complexes are the basis for listing 11 solid waste streams as hazardous wastes under RCRA (EPA 19860. According to RCRA, cyanide-containing wastes are required to be treated by the best available technology before the wastes are disposed of in land. Cyanogen- and cyanogen chloride-containing waste, for example, are assigned the hazardous waste codes PO31 and P033, respectively, and must be treated by chemical or electrolytic oxidation employing specific oxidizing reagents (e.g., hypochlorite, peroxides, ozone or ultraviolet light assisted ozone) or other reagents of equivalent efficiency; wet air oxidation incorporating a surrogate or indicator parameter; or treatment by incineration in units operated in compliance with RCRA standards (EPA 1986f). The concentration of cyanide permissible in wastes for land disposal vary according to the nature of wastes. The maximum concentration in treated waste (i.e., non-waste water) should not exceed 590 mg/kg for total cyanides and 30 mg/kg for cyanides amenable to chlorination (EPA 1988c). While liquids are prohibited from land disposal, the maximum concentrations allowable in most treated waste waters, with the exception of the bottom streams from the acetonitrile

column and the waste water stripper used in the production of acrylonitrile, are 1.9 mg/L for total cyanides and 0.86 mg/kg for cyanides amenable to chlorination (EPA 1988c).

Conducted in the presence of sodium hydroxide or sodium hypochlorite, the chemical oxidation method commonly referred to as alkaline chlorination is the most widely used commercial method for treating cyanide-containing wastes, This method results in the conversion of the cyanide solution to the less toxic cyanate. Depending on the cyanides present, the product will be a sludge or solution, which when sufficient reaction time has been allowed, will largely be devoid of free cyanide (IRPTC 1985). Cyanide salts should not be treated with acid in preparation for disposal or flushed into drains which may contain or subsequently receive acid waste. Acidification is not a recommended method of treatment prior to disposal because of the liberation of hydrogen cyanide. Similarly, incineration of cyanides must proceed with caution and is not recommended unless extensive equipment capable of safely handling liberated hydrogen cyanide is available (IRPTC 1985). Of the cyanide compounds included in this profile, only hydrogen cyanide and cyanogen chloride are listed as potential candidates for rotary kiln incineration or fluidized bed incineration (HSDB 1996).

The biodegradation of cyanides has been investigated, with varying results, for several industrial processes, and additional research in this area is needed. While investigations of the potential for microbial species found in mineral processing waste waters demonstrate effective removal of cyanide, metal complexed cyanide, and thiocyanate (Boucabeille 1994b), complex cyanides did not appear amenable to biodegradation at gasworks sites (Thomas and Lester 1993). Formaldehyde in basic solution can convert free cyanide to substituted acetates. Copper and silver in electroplating wastes can be recovered as free metals with formaldehyde reduction. The complexes of zinc and cadmium can be recovered as the oxides with formaldehyde treatment. Calcium or sodium polysulfide treatment converts some cyanide wastes into less toxic thiocyanate. These examples suggest that typical treatments involve the decomposition of cyanides to less toxic compounds by physical or chemical processes. More than 97% of cyanide is typically removed from waste waters by alkaline chlorination, electrolysis, or ozonation process. Cyanide from some wastes can be removed by ion-exchange resins. After using an appropriate treatment method, cyanide wastes may be disposed of in a secured sanitary landfill (Grosse 1986; Higgins and Desher 1988; Tucker and Carson 1985). The possibility of disposal by injection of high-pH cyanide wastes into sandstone has also been investigated (Scrivner et al. 1986). It appears that in 19920.8 million pounds of hydrogen cyanide were disposed of by underground injection (see Section 5.2) (TR193 1995).

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Anthropogenic sources are responsible for much of the cyanide in the environment. Cyanide also occurs naturally in the fruits, seeds, roots, and leaves of numerous plants, and is released to the environment from natural biogenic processes from higher plants, bacteria, and fungi (Cicerone and Zellner 1983; Crutzen and Carmichael 1993; Fiksel et al. 1981; Knowles 1988). However, an estimate of the amount of cyanide released to the environment from natural biogenic processes is not available. The major cyanide releases to water are discharges from metal-finishing industries, iron and steel mills, and organic chemical industries (Fiksel et al. 1981). Effluents from the cyanidation process used in precious metal extraction contain high amounts of cyanide (Huiatt 1985; Scott 1985). The contribution of this source to the total cyanide discharge in water, however, is insignificant (Fiksel et al. 1981). Vehicle exhaust (Fiksel et al. 1981) and biomass burning (Crutzen and Carmichael 1993; Lobert and Warnatz 1993) are major sources of cyanide released into the air. The major sources of simple and complex cyanide releases to soil appear to be disposal of cyanide wastes in landfills and the use of cyanide-containing road salts (Fiksel et al. 198 1; Gaffney et al. 1987). Cyanogen chloride is formed in drinking water from reaction of humic substances with chloramine produced during chlorination (Jacangelo et al. 1989; Ohya and Kanno 1987).

Thiocyanate is released to water primarily from discharges of industrial waste waters from coal processing and extraction of gold and silver (Boucabeille et al. 1994a). Thiocyanate is also found in mining waste waters where it results from the interaction of free cyanide with sulphur (Boucabeille et al. 1994b). Releases of thiocyanate to soil result from anthropogenic and natural sources. Anthropogenic releases occur primarily from direct application in herbicidal formulations and from disposal as byproducts from industrial processes. Nonanthropogenic sources include damaged or decaying tissues of plants from the family *Brassica* (e.g., cabbage, mustard, kale) (Brown and Morra 1993).

Cyanide (reported as cyanide, hydrogen cyanide, sodium cyanide, potassium cyanide, or copper(I) cyanide) has been identified in at least 406 of 1,428 current or former hazardous wastes sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 1996). However, the number of sites evaluated for cyanide is not known. The frequency of these sites within the United States can be seen in Figure 5- 1.

Figure 5-1. Frequency of NPL Sites with Cyanide Contamination

SITES
1-3
4-6
7-15
16-33

Derived from HazDat 1996

5. POTENTIAL FOR HUMAN EXPOSURE

Cyanide is released into air mainly as hydrogen cyanide gas and, to a lesser extent, as particulate cyanides. Hydrogen cyanide can potentially be transported over long distances before reacting with photochemically generated hydroxyl radicals. The residence time of hydrogen cyanide in the atmosphere has been estimated to be approximately 2.5 years, with a range of 1.3-5.0 years, depending on the hydroxyl radical concentration (Cicerone and Zellner 1983). Neither photolysis nor deposition by rainwater is expected to be a significant removal mechanism. Only 2% of the tropospheric hydrogen cyanide is expected to be transported to the stratosphere (Cicerone and Zellner 1983). In water, cyanide occurs most commonly as hydrogen cyanide. Hydrogen cyanide and soluble metal cyanides are expected to be removed from water primarily by volatilization. At low concentrations, some cyanide may also be removed by aerobic or anaerobic biodegradation (Callahan et al. 1979). At soil surfaces, volatilization of hydrogen cyanide is a significant loss mechanism for cyanides. In subsurface soil, cyanide at low concentrations would probably biodegrade under both aerobic and anaerobic conditions. In cases where cyanide levels are toxic to microorganisms (i.e., landfills, spills), water-soluble cyanides may leach into groundwater.

The environmental fate of thiocyanate has not been thoroughly investigated. Aerobic and anaerobic biodegradation are significant transformation processes for thiocyanates in water (Boucabeille et al. 1994a, 1994b; Shivaraman et al. 1985) and soil (Brown and Morra 1993). At near-ambient temperatures, sorption and volatilization are not significant partitioning processes for thiocyanate in soil (Brown and Morra 1993).

Despite the various ways cyanide is thought to be released into the environment, available monitoring data are limited. It appears that the general population is exposed to cyanide primarily by ingestion of foods that contain cyanides and, to a lesser extent, by consumption of contaminated drinking water and inhalation of contaminated air. Dermal absorption is not a significant exposure route for the general population. The concentration of cyanide in the northern hemisphere's non-urban troposphere ranges from 160 to 166 ppt (ppt = parts per trillion) (Cicerone and Zellner 1983; Jaramillo et al. 1989). The mean cyanide concentration in most surface waters is not greater than 3.5 ug/L (Fiksel et al. 1981). The cyanogen chloride concentration in drinking water is 0.45-0.80 µg/L (Krasner et al. 1989). The cyanide content in certain varieties of lima beans can be as high as 3 mg/g (Honig et al. 1983), although values between 0.10 and 0.17 mg/g are common in U.S. lima beans (Towill et al. 1978). Much lower cyanide concentrations in various cereal grains and cereal products have been reported, ranging from 0.001 to 0.45 µg/g (Honig et al. 1983). Mean cyanide concentrations in soybean products have been found to range from 0.07 to 0.3 µg/g; whereas, the mean cyanide concentration in soybean hulls was 1.24 µg/g (Honig et

5. POTENTIAL FOR HUMAN EXPOSURE

al. 1983). Due to the lack of data on cyanide content in total diet samples, the average daily intake could not be estimated.

Available monitoring data on thiocyanate are also very limited. No information was found in the available literature on major routes of exposure among the general population or on estimates of exposure. Because thiocyanate is a major metabolite of cyanide in the body, exposure to cyanide is a source of thiocyanate exposure. Thiocyanate occurs naturally in many edible plants. Vegetables in the family *Brassica* contain high levels of thiocyanate with concentrations ranging up to 660 µg/g, whereas other commonly consumed vegetables (e.g., spinach, radishes, celery) generally contain thiocyanates at concentrations <2 µg/g. Thiocyanate concentrations in milk and other dairy products and in meat have been reported to range from <1 to 9.0 µg/g and 0.5 to 0.7 µg/g, respectively (Weuffen et al. 1984). Thiocyanate concentrations in coal plant waste waters (Jensen and Tuan 1993) and mining waste waters (Boucabeille et al. 1994b) have been found to range from 100 to 1,500 mg/L and 300 to 450 mg/L, respectively. No data could be found in the available literature on thiocyanate concentrations in surface, ground, or drinking waters. Soils treated with rapeseed meal (from the family *Brassica)* contained thiocyanate at concentrations on the order of 6 µg/g (Brown et al. 1991).

It should be noted that the amounts of cyanide or thiocyanate found by chemical analysis are not necessarily the amounts that are bioavailable.

Among the general population, subpopulations with the most likely potential of exposure to cyanide at concentrations higher than background levels include active and passive tobacco smokers (Fiksel et al. 1981) and individuals who are exposed to house or other types of building fires (Andrews et al. 1989). Subpopulations with potential for exposure to cyanides or thiocyanates are residents who live near industrial sites releasing these compounds to the environment, residents who live near cyanide- or thiocyanate-containing hazardous waste sites, and people who consume foods, high in cyanogenic glycosides. Fetuses of smoking mothers or mothers exposed to high levels of environmental smoke may also be at risk of exposure to relatively high concentrations of cyanide and thiocyanate (Bottoms et al. 1982; EPA 1992f; Hauth et al. 1984).

Occupational exposures to cyanide occur primarily through inhalation and, less frequently, through dermal absorption. Estimates from the National Occupational Exposure Survey (NOES) conducted by the National Institute for Occupational Safety and Health (NIOSH) indicate that over 250,000 workers are potentially exposed to cyanide compounds, including cyanogen chloride and ammonium thiocyanate

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(NIOSH 1989a). Workers may be exposed to cyanides in various occupations, including electroplating, metallurgy, pesticide application, firefighting, steel manufacturing, gas works operations, and metal cleaning (Fiksel et al. 1981). The manufacture of industrial inorganic chemicals may be a potential source of occupational exposure to cyanogen chloride (NIOSH 1989a). Potential sources of occupational exposure to ammonium thiocyanate include the manufacture of electronic computing equipment, research and development laboratories, newspaper and other commercial printing, general medical and surgical hospitals, production of adhesives and sealants, and the construction and furniture industries (NIOSH 1989a). Potential occupational exposures may also occur during the direct application of herbicidal formulations (e.g., amitrol-T, a mixture of ammonium thiocyanate and amino-l ,2,4-triazole) and from handling, treatment, or disposal of thiocyanate-containing wastes from industrial processes (Brown and Morra 1993).

5.2 RELEASES TO THE ENVIRONMENT

5.2.1 Air

Cyanide emissions into the air have been conservatively estimated at 44 million pounds a year based on data obtained during the mid-to-late 1970s. Over 90% of these emissions were attributed to releases from automobile exhaust. The second largest source of cyanide emission to the air was reported to be from the manufacture of methyl methacrylate, acrylonitrile, and hydrogen cyanide (Fiksel et al. 1981). More recent quantitative data regarding total cyanide emissions were not located in the available literature. Other smaller sources of cyanide release include emissions from iron and steel production, coal combustion (Fiksel et al. 1981), petroleum refineries (Fiksel et al. 1981), oil shale retorting processes (Hargis et al. 1986; Sklarew and Hayes 1984), municipal solid waste incinerators (Carotti and Kaiser 1972; Greim 1990), the combustion of acrylonitriles or other nitrogen-containing plastics (Brandt-Rauf et al. 1988; Fiksel et al. 1981), cigarette smoke (Baker and Proctor 1990; Fiksel et al. 1981; Guerin et al. 1987), volatilization from cyanide waste disposed of in landfills, and direct release to the atmosphere from certain agricultural pest control activities (Fiksel et al. 1981). In 1976, an estimated 137,000 pounds of cyanide was released in the air from agricultural pest control, 18,000-180,000 pounds from incineration, and 13,000-750,000 pounds from cigarette smoke (Fiksel et al. 1981). The production of coke or other coal carbonization processes also release hydrogen cyanide into the atmosphere (Cicerone and Zellner 1983). Hydrogen cyanide is also released into the atmosphere from natural biogenic processes from higher plants, bacteria, and fungi (Cicerone and Zellner 1983; Crutzen and Carmichael 1993; Fiksel et al. 1981; Knowles 1988). However, an estimate of the amount of hydrogen cyanide released from natural biogenic sources is

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not available (Cicerone and Zellner 1983). Crutzen and Carmichael (1993) have recently suggested that biomass burning represents an important source of atmospheric hydrogen cyanide. The combined worldwide emissions of hydrogen cyanide and acetonitrile due to biomass burning have been estimated to range from 0.5 to 1.7×10^{12} g of N/year ($\approx$ 1.1- 3.7 billion pounds per year) (Crutzen and Andreae 1990). These estimates were based in part on highly uncertain global estimates of worldwide amounts of burned fuel and area and, consequently, have a high degree of uncertainty. Lobert and Warnatz (1993) have estimated that low molecular weight nitriles, primarily hydrogen cyanide and acetonitrile, represent about 4% of the nitrogen balance of biomass fires and contribute a major amount to their global atmospheric source.

The amount of hydrogen cyanide released to the atmosphere in 1993 by U.S. industrial facilities sorted by state is given in Table 5-l (TR193 1995). According to TR193 (1995), an estimated total of 2.23 million pounds (approximately 1,010 metric tons) of hydrogen cyanide, amounting to approximately 73.1% of the total environmental release, was discharged to the air from manufacturing and processing facilities in the United States in 1993. The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. No information is available in the TRI database for other cyanide and thiocyanate compounds in this profile because these compounds are not included under SARA, Title III, and therefore, are not among the chemicals that facilities are required to report (EPA 19938).

Cyanides (reported as cyanide, hydrogen cyanide, sodium cyanide, potassium cyanide, calcium cyanide, or copper(I) cyanide) have been detected in air samples collected at 5 of the 406 hazardous waste sites where cyanides have been detected in some environmental medium (HazDat 1996). The HazDat information used includes data from both NPL and other Superfund sites. No information was found on detections of cyanogen, cyanogen chloride, or thiocyanates in air at any NPL or other Superfund hazardous waste sites (HazDat 1996).

5.2.2 Water

There are numerous sources that release cyanide into water. Cyanide is released into water from both point and nonpoint sources. The major point sources of cyanide released to water are discharges from publicly owned treatment works (POTWs), iron and steel production, and organic chemical industries (Fiksel et al. 1981). Estimates based on data from the mid-to-late 1970s indicate that these sources account for $\approx$ 89% of the estimated 31 million pounds of total cyanide discharged annually to surface

Table 5-1. Releases to the Environment from Facilities That Manufacture or Process Hydrogen Cyanide

State[a]	City	Facility	Reported amounts released in pounds per year						
			Air	Water	Land	Underground injection	Total environment[b]	POTW transfer	Off-site waste transfer
AL	THEODORE	DEGUSSA CORP.	12,926				12,926		396
AL	THEODORE	VEBA CORP.	500				500	250	250
CA	SACRAMENTO	MITSUBISHI RAYON CO. LTD.	62,741				62,741		
CA	WILMINGTON	ULTRAMAR CORP.	30,500				30,500		
IL	CHICAGO	PMC INC.	10				10		
KY	ASHLAND	NA	5				5		
KY	ASHLAND	NA	10				10		
LA	FRANKLIN	CABOT CORP.	763,550				763,550		
LA	PLAQUEMINE	DOW CHEMICAL CO.	350				350		
LA	ST. GABRIEL	CIBA-GEIGY CORP.	327	136			463		11
LA	VILLE PLATTE	CABOT CORP.	589,750				589,750		
LA	WESTWEGO	NA	2,120				2,120		
MN	ROSEMOUNT	KOCH IND. INC.	120	260			380		
NH	NASHUA	HAMPSHIRE HOLDINGS CORP.	1,841				1,841		17
OH	LIMA	ARCADIAN CORP.	39,400				39,400		
OH	LIMA	HAMPSHIRE CHEMICAL CORP.	12				12		3
PA	WILLIAMSPORT	LONZA INC.	112				112	7	
SC	ORANGEBURG	ALBEMARLE CORP.	18,250				18,250		
SC	PIEDMONT	AMOCO CHEMICAL CO.	20,000				20,000	24	
SC	ROCK HILL	BASF CORP.	24,250				24,250		

Table 5-1. Releases to the Environment from Facilities That Manufacture or Process Hydrogen Cyanide (continued)

			Reported amounts released in pounds per year						
State[a]	City	Facility	Air	Water	Land	Underground injection	Total environment[b]	POTW transfer	Off-site waste transfer
TN	MEMPHIS	E. I. DU PONT DE NEMOURS & CO.	45,734				45,734		
TN	MEMPHIS	ICI AMERICAS INC.	6,346				6,346		
TN	ROCKWOOD	AKZO NOBEL NV	12,560				12,560		
TX	ALVIN	MONSANTO CO.	10,700			170,000	180,700		
TX	BEAUMONT	E. I. DU PONT DE NEMOURS & CO.	9,530				9,530		
TX	DEER PARK	ROHM & HAAS CO.	203,203				203,203		
TX	DEER PARK	NA	280			1,268	1,548		
TX	DEER PARK	W. R. GRACE & CO.-CONN.							33
TX	FREEPORT	DOW CHEMICAL USA	11,026				11,026		
TX	HOUSTON	ISK ENTERPRISES CORP.	173				173		9
TX	NEDERLAND	ICI ACRYLICS INC.	1,450				1,450		2,050
TX	ORANGE	E. I. DU PONT DE NEMOURS & CO.	44,243			527,322	571,565		
TX	PAMPA	CABOT CORP.	152,586				152,586		
TX	PORT LAVACA	BP AMERICA	48,200				48,200		
TX	TEXAS CITY	NA	11,520				11,520		
TX	VICTORIA	E. I. DU PONT DE NEMOURS & CO.	10,782		12	123,225	134,019		41
UT	MAGNA	HERCULES INC.	52,978				52,978		

Table 5-1. Releases to the Environment from Facilities That Manufacture or Process Hydrogen Cyanide (continued)

State[a]	City	Facility	Reported amounts released in pounds per year						
			Air	Water	Land	Underground injection	Total environment[b]	POTW transfer	Off-site waste transfer
WI	SUPERIOR	MURPHY OIL USA INC.	44,192				44,192		
WV	WAVERLY	CABOT CORP.	1,634				1,634		
WY	GREEN RIVER	FMC CORP.	30				30		
		Totals	2,233,941	396	12	821,815	3,056,164	281	2,810

Source: TRI93 1995

[a] Post office state abbreviations used
[b] The sum of all releases of the chemical to air, land, water, and underground injection wells by a given facility

NA = not available; POTW = publicly owned treatment works

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waters. Since metal finishing and organic chemical industries are estimated to account for 90% of the influent to POTWs, they are the dominant sources of both direct and indirect discharge of cyanide to water (Fiksel et al. 1981). The amount of cyanide released to surface water and POTWs by U.S. industrial facilities that manufactured or processed cyanide compounds ranged from approximately 0 to 150,000 and 1,100 to 1,090,000 pounds, respectively (TR188 1990). These data indicate that the industrial discharge of cyanides into surface water and POTWs decreased substantially in 1988 in comparison to the estimated discharge during the 1970s. The amount of hydrogen cyanide released to surface water and POTWs in 1993 by U.S. industrial facilities sorted by state is shown in Table 5-l (TR193 1995). According to TR193 (1995), estimated totals of 396 and 281 pounds of hydrogen cyanide were discharged to surface water and POTWs, respectively, in 1993. These combined releases amount to approximately 0.01% of the total environmental release of hydrogen cyanide. The TRI data should be used with caution since only certain facilities are required to report. This is not an exhaustive list. No information is available in the TRI database for other cyanide and thiocyanate compounds in this profile because these compounds are not included under SARA, Title III, and therefore, are not among the chemicals that facilities are required to report (EPA 1993g).

The effluents from the cyanidation process used in the extraction of precious metals from their ores may contain high levels of cyanide (Huiatt 1985; Scott 1985). The total cyanide content of typical tailing pond effluents from gold mill tailing ponds has been reported to range from 0.3 to 61 mg/L (Scott 1985). However, the contribution from this source to the total discharge of cyanide has been estimated to be negligible (Fiksel et al. 1981). Leachates from solid waste disposal sites are point sources of cyanide release to groundwater (Myers 1983; Venkataramani et al. 1984). No quantitative estimate of the amount of cyanide entering the groundwater from this point source was located. The nonpoint sources of cyanide released to water are comprised of agricultural and road runoff and atmospheric fallout and washout. The predominant sources of cyanides found in urban runoff samples were reported to be products of gasoline combustion and anticaking ingredients in road salts (Cole et al. 1984). It has been estimated that a maximum of ≈ 2 million pounds of sodium ferrocyanide that is used as an anticaking agent in road salts during the winter in the northeastern United States are washed off from roads into streams and storm sewers (Fiksel et al. 1981; Gaffney et al. 1987).

Cyanides (reported as cyanide, hydrogen cyanide, sodium cyanide, potassium cyanide, calcium cyanide, or copper(I) cyanide) have been detected in surface water samples at 117 of the 406 hazardous waste sites, in groundwater samples at 208 of the 406 hazardous waste sites, and in leachate samples at 43 of the

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406 hazardous waste sites where cyanides have been detected in some environmental medium (HazDat 1996). The HazDat information used includes data from both NPL and other Superfund sites.

Cyanogen chloride is formed in drinking water from the reaction of humic substances with chloramine formed during chlorination (Jacangelo et al. 1989; Ohya and Kanno 1987). In a mid-l 970s EPA survey, cyanogen chloride was detected in drinking water from 8 of 10 U.S. cities (Fielding and Packham 1977). No information could be found in the available literature on the release of cyanogen to water. No information was found on detections of cyanogen or cyanogen chloride in surface or groundwater at any NPL or other Superfund hazardous waste sites (HazDat 1996).

Thiocyanate is released to water primarily from discharges of industrial waste waters from coal processing and extraction of gold and silver (Boucabeille et al. 1994a). Thiocyanate is also found in mining waste waters where it results from the reaction of free cyanide with sulphur (Boucabeille et al. 1994b). Thiocyanate has been detected in surface water samples at two of the eight hazardous waste sites, and in groundwater samples at five of the eight hazardous waste sites where thiocyanate has been detected in some environmental medium (HazDat 1996). The HazDat information used includes data from both NPL and other Superfund sites.

5.2.3 Soil

Estimates of amounts of cyanide released to soil from anthropogenic sources were not located. The largest anthropogenic sources of cyanide releases to soil probably result from the disposal of cyanide wastes in landfills and the use of cyanide-containing road salts (Fiksel et al. 1981; Gaffney et al. 1987). The amount of hydrogen cyanide released to land in 1993 by U.S. industrial facilities sorted by state is shown in Table 5-l (TR193 199). According to TR193 (1995), an estimated total of only 12 pounds of hydrogen cyanide, a negligible amount of the total environmental release, was discharged to land from U.S. manufacturing or processing facilities in 1993. However, some of the estimated 2,810 pounds of hydrogen cyanide wastes transferred off-site (see Table 5-l) may be ultimately disposed of in land. The TRI data should be used with caution since only certain facilities are required to report. This is not an exhaustive list. No information is available in the TRI database for other cyanide and thiocyanate compounds in this profile because these compounds are not included under SARA, Title III, and therefore, are not among the chemicals that facilities are required to report (EPA 19938).

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Natural biogenic processes of bacteria, fungi, and cyanogenic plants such as sorghum, soybeans, and cassava, also release cyanide into the soil (Knowles 1988; Towill et al. 1978; WHO 1992). Cyanides (reported as cyanide, hydrogen cyanide, sodium cyanide, potassium cyanide, calcium cyanide, or copper(I) cyanide) have been detected in soil samples at 187 of the 406 hazardous waste sites, in sediment samples at 97 of the 406 hazardous waste sites, and in soil gas samples at 1 of the 406 hazardous waste sites where cyanides have been detected in some environmental medium (HazDat 1996). The HazDat information used includes data from both NPL and other Superfund sites.

Cyanogen has been detected in soil samples at the one hazardous waste site where cyanogen has been found (HazDat 1996). Cyanogen chloride has been detected in soil samples at one of the two hazardous waste sites where this compound was detected in some medium (HazDat 1996). The HazDat information used includes data from both NPL and other Superfund sites. No other information could be found in the available literature on the release of cyanogen or cyanogen chloride to soil.

Releases of thiocyanate to soil result from anthropogenic and natural sources. Anthropogenic releases occur primarily from direct application in herbicidal formulations (e.g., amitrol-T, a mixture of ammonium thiocyanate and amino-l ,2,4-triazole) and from disposal as byproducts from industrial processes. Nonanthropogenic sources include damaged or decaying tissues of plants from the family Brussica (e.g., mustard, rape) (Brown and Morra 1993). Thiocyanate has been detected in soil samples collected at 2 of the 8 hazardous waste sites, and in sediment samples at 3 of the 8 hazardous waste sites where thiocyanate has been detected in some medium (HazDat 1996). The HazDat information used includes data from both NPL and other Superfund sites.

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

Because hydrogen cyanide is a gas and has a reIativeIy slow degradation rate in air (see Section 5.3.2), the atmosphere will be the ultimate sink for this compound. Almost all of the hydrogen cyanide released to the atmosphere remains in the lower altitudes (troposphere); only 2% of tropospheric hydrogen cyanide is transferred to the stratosphere (Cicerone and Zellner 1983). Cyanide has the potential to be transported over long distances from its emission source. Despite higher water solubility at saturated pressure, the removal of hydrogen cyanide by rainwater appears to be a negligible partitioning pathway (Cicerone and Zellner 1983). Because hydrogen cyanide is a gas, its removal from air by dry deposition is also likely to

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be negligible. However, metal cyanide particles, particularly water-soluble cyanide particles, are expected to be removed from the air by both wet and dry deposition.

Volatilization and sorption are the two physical processes that contribute to the loss of cyanide from water. At pH <9.2, most of the free cyanide in solution should exist as hydrogen cyanide, a volatile cyanide form (Towill et al. 1978). On the basis of Henry's law constant (see Table 3-2) and the volatility characteristics associated with various ranges of Henry's law constant (Thomas 1982), volatilization is a significant and probably dominant fate process for hydrogen cyanide in surface water (EPA 1992f). The most common alkali metal cyanides (e.g., sodium and potassium cyanide) may also be lost from surface water primarily through volatilization; whereas, the sparingly soluble metal cyanides such as copper (I) cyanide are removed from water predominantly by sedimentation and biodegradation (see Section 5.3.2.2) (EPA 1992f). Variations in the volatilization rate are expected because this process is affected by several parameters including temperature, pH, wind speed, and cyanide concentration (Callahan et al. 1979). Callahan et al. (1979) summarized the unpublished results of a laboratory study which indicated that the volatilization half-life of hydrogen cyanide from solutions at concentrations of 25-200 μg/L ranged from 22 to 110 hours. First order kinetics were observed. In outdoor experiments with moderate winds the rate of hydrogen cyanide loss increased by a factor of 2-2.5. In a study to evaluate the effect of cyanide on biochemical oxidation, there was a 50% loss of 6 ppm (mg/L) cyanide in river water kept in open biochemical oxygen demand bottles (without aeration) at pH 7.4 within ≈ 10 days (Ludzack et al. 1951). When the bottles were aerated (rate of aeration not given), 50% loss occurred in only ≈ 10 hours. The kinetics of the rate of loss due to volatilization were not rigorously investigated. The volatilization rate was pH-dependent, with the rate faster at a lower pH. Data indicated that volatilization is a more important fate process than cyanide loss due to chemical and biodegradation reactions (see Section 5.3.2.2) (Ludzack et al. 1951; Raef et al. 1977a). Because volatilization is not an important fate process for cyanide in groundwater, cyanide would be expected to persist for considerably longer periods of time in underground aquifers than in surface water.

Cyanides are sorbed by various natural media, including clays (Cruz et al. 1974), biological solids (Raef et al. 1977b), and sediments (Callahan et al. 1979). However, additional data are necessary to assess the significance of cyanide sorption to suspended solids and sediments in water. Hydrogen cyanide and the alkali metal cyanides are not likely to be strongly sorbed onto sediments and suspended solids because of their high water solubilities (see Table 3-2). Soluble metal cyanides may show somewhat stronger sorption than hydrogen cyanide, with the extent of sorption increasing with decreasing pH and increasing iron oxide, clay, and organic material contents of sediment and suspended solids (Callahan et al. 1979).

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However, sorption is probably insignificant even for metal cyanides when compared to volatilization and biodegradation (Callahan et al. 1979; EPA 1992f).

There are no data available to indicate that simple metal cyanides and hydrogen cyanide bioconcentrate in aquatic organisms (ASTER 1994; Callahan et al. 1979; EPA 1980a, 1985a, 1992f). Bioconcentration factors (BCFs) of 0.73 and 1.62 can be calculated for hydrogen cyanide, using the equation of Veith et al. (1979) for the BCF of a chemical in whole fish (log BCF = 0.85 log K_{ow} -0.70) and the log K_{ow} values in Table 3-2. Similarly, the calculated BCF for sodium cyanide is 0.47. There is some evidence that metal cyanide complexes bioaccumulate in aquatic organisms. Fish from water with soluble silver and copper cyanide complexes were found to have metal cyanides in their tissues at concentrations ranging up to 168 and 304 µg/g, respectively (wet or dry weight not specified) (Callahan et al. 1979). However, the bioconcentration factors for such compounds in fish tissues are not known (ASTER 1994). It is difficult to evaluate the toxicologic significance of bioaccumulation of metal cyanide complexes because these compounds are much less toxic than soluble hydrogen cyanide, sodium cyanide, or potassium cyanide (EPA 1992f). There is no evidence of biomagnification of cyanides in the food chain (Towill et al. 1978). Volatilization of hydrogen cyanide would be a significant loss mechanism for cyanides from soil surfaces at a pH < 9.2. Cyanides are fairly mobile in soil. Mobility is lowest in soils with low pH and high concentrations of free iron oxides, positively charged particles, and clays (e.g., chlorite, kaolin, gibbsite), and highest in soils with high pH, high concentrations of free $CaCO_3$ and negatively charged particles, and low clay content (Callahan et al. 1979). Although cyanide has a low soil sorption capability, it is usually not detected in groundwater, probably because of fixation by trace metals through complexation or transformation by soil microorganisms (see Section 5.3.2.3) (Towill et al. 1978). In soils where cyanide levels are high enough to be toxic to microorganisms (i.e., landfills, spills), this compound may leach into groundwater (EPA 1984a). The possibility of cyanide leaching into groundwater under certain conditions is confirmed by the detection of cyanides in groundwater samples from solid waste sites (Anonymous 1990; Myers 1983; Venkataramani et al. 1984).

No information could be found in the available literature on the transport and partitioning of cyanogen or cyanogen chloride in the environment, or on their partitioning coefficients (K_{oc} K_{ow}) or Henry's law constants (see Table 3-2). Because these compounds are highly volatile gases (see Table 3-2), it would be expected that volatilization from water and soil would be a primary route of environmental partitioning. However, cyanogen is extremely reactive and does not persist in the environment unchanged (Towill et al. 1978).

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Similarly, little information could be found in the available literature on the environmental transport and partitioning of thiocyanate in the environment. At near ambient temperatures ($\approx$ 30 °C), it appears that sorption and volatilization are not significant partitioning processes for thiocyanate in soil, with thiocyanate losses due primarily to microbial degradation (see Section 5.3.2.3) (Brown and Morra 1993).

5.3.2 Transformation and Degradation

The various cyanide compounds included in this profile undergo a number of different transformation and degradation reactions in the environment as discussed in the following sections. The resulting environmental transformation products within different media are shown in Table 5-2.

5.3.2.1 Air

Most cyanide in the atmosphere exists almost entirely as hydrogen cyanide gas, although small amounts of metal cyanides may be present as particulate matter in the air (EPA 1984a). Hydrogen cyanide is very resistant to photolysis at wavelengths of normal sunlight (Callahan et al. 1978). The most important reaction of hydrogen cyanide in air is the reaction with photochemically generated hydroxyl radicals and subsequent rapid oxidation to carbon monoxide (CO) and nitric oxide (NO); photolysis and reaction with ozone are not important transformation processes, and reaction with singlet oxygen ($0\ ^1D$) is not a significant transformation process except at stratospheric altitudes where singlet oxygen is present in significant concentrations (Cicerone and Zellner 1983). The rate of hydroxyl radical reaction with hydrogen cyanide in the atmosphere depends on the altitude, and the rate of the reaction is at least an order of magnitude faster at lower tropospheric altitudes (0-8 km) than at upper tropospheric altitudes (10-12 km) (Cicerone and Zellner 1983). Based on a reaction rate constant of 3×10^{-14} cm^3/(molecule-sec) at 25 °C (Fritz et al. 1982) and assuming an average hydroxyl radical concentration of 5×10^5 molecules/cm^3, the residence time for the reaction of hydrogen cyanide vapor with hydroxyl radicals in the atmosphere is $\approx$ 2 years. This value compares well with the atmospheric residence time derived by Cicerone and Zellner (1983) of approximately 2.5 years, with a range of 1.3-5.0 years, depending on the hydroxyl radical concentrations assumed. Using the equation $t_{1/2} = 0.693\tau$ for converting residence time (τ) to half-life ($t_{1/2}$) (Lyman 1982) and an estimated atmospheric residence time for hydrogen cyanide of 2-3 years, and assuming first-order kinetics for the reaction of hydrogen cyanide with hydroxyl radicals, an atmospheric half-life of 1.4-2.9 years can be calculated for hydrogen cyanide.

Table 5-2. Environmental Transformation Products of Cyanide Compounds by Medium

Parent compound	Product(s)	Comments	Reference
Air			
HCN	$HOCN + HO_2$ (unlikely) $NO + CHO^-$ (formed in minutes)	$HNC \cdot OH$ intermediate	Cicerone and Zellner 1983
	$NO + CHO^-$ (formed in minutes)	$HCN \cdot OH$ intermediate	Cicerone and Zellner 1983
Cyanogen	HCN, cyanic acid (NCOH), and other compounds	In the presence of water; slow reaction	Callahan et al. 1979
Water			
HCN	$NH_4^+ + HCOO^-$ in equilibrium with $H_2NCHO + H_2$	pH dependent ($pH < 1$, $t_{1/2} = 10–1,000$ h)	Callahan et al. 1979
	$NH_4^+ + HCOO^-$	Alkaline hydrolysis; very slow reaction	
CN^-	Metal cyanides	In the presence of excess metals; alkali metal cyanides very soluble; alkaline earth metal cyanides not very soluble	Callahan et al. 1979; EPA 1992f
	Complex metallocyanides	Excess CN^- in the presence of metals; solubilities of metallocyanides vary	Callahan et al. 1979; EPA 1992f
	>99% HCN	$pH < 7$	Towill et al. 1978
CN^-	$NH_3 + CO_2$ (NH_3 converted to nitrite and nitrate in presence of nitrifying bacteria)	Aerobic biotransformation	Richards and Shieh 1989
	$N_2 + CO_2$	Anaerobic biotransformation under denitrification conditions	Richards and Shieh 1989
HCN/CN^- salts	Thiocyanate (SCN^-), $NH_3 + CO_2$, $CHOO^-$	Biotransformation	Towill et al. 1978
Cyanogen	HCN, cyanic acid (NCOH), and other compounds	Slow reaction	Callahan et al. 1979
Metallocyanides	CN^- (possibly)	Photolysis	Callahan et al. 1979
	Isocyanate (OCN^-)	Oxidation	EPA 1992f
	$CO_2 + N_2$	In the presence of strong oxidizing agents	EPA 1992f
SCN^-	HCN	In acidic media	Callahan et al. 1979

Table 5-2. Environmental Transformation Products of Cyanide Compounds by Medium (continued)

Parent compound	Product(s)	Comments	Reference
Sediment and Soil			
CN^-	Metallocomplexes	Abiotic transformation in the presence of metals	Towill et al. 1978
	$NH_3 + CO_2$ (NH_3 converted to nitrite and nitrate in presence of nitrifying bacteria)	Aerobic biotransformation (predicted from fate in wastewater)	Richards and Shieh 1989
	$N_2 + CO_2$	Aerobic biotransformation under denitrification conditions (predicted from fate in wastewater)	Richards and Shieh 1989
SCN^-	COS (possibly; microbial degradation pathway not known)	Microbial degradation	Brown and Morra 1993
Wastewater/Sludge			
CN^-	$NH_3 + CO_2$ (NH_3 converted to nitrite and nitrate in presence of nitrifying bacteria)	Aerobic biotransformation	Richards and Shieh 1989
	$N_2 + CO_2$	Anaerobic biotransformation under denitrification conditions	Richards and Shieh 1989
CN^-/metallo-cyanides (including cuprocyanide)	$NH_3 + CO_2$	Microbial degradation in mining wastewaters	Boucabeille et al. 1994b
SCN^-	$NH_3 + CO_2 + SO_4^=$	Microbial degradation in mining wastewaters	Boucabeille et al. 1994a
	$COS + NH_3$	Microbial degradation in activated sludge	Katayama et al. 1993

h = hours

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Cyanogen is extremely reactive and does not persist in the environment unchanged (Towill et al. 1978). However, no specific information was found in the available literature on the transformation and degradation of cyanogen, or cyanogen chloride, in air. Cyanogen does react slowly with water to yield hydrogen cyanide and cyanic acid (HOCN) among other products (Callahan et al. 1979) and this hydrolysis reaction may be a possible atmospheric degradation pathway.

No information was found in the available literature on the transformation and degradation of thiocyanates in air.

5.3.2.2 Water

Cyanide occurs most commonly as hydrogen cyanide in water, although it can also occur as the cyanide ion, alkali and alkaline earth metal cyanides (potassium cyanide, sodium cyanide, calcium cyanide), relatively stable metallocyanide complexes (ferricyanide complex $[Fe(CN)_6]^{-3}$), moderately stable metallocyanide complexes (complex nickel and copper cyanide), or easily decomposable metallocyanide complexes (zinc cyanide $[Zn(CN)_2]$, cadmium cyanide $[Cd(CN)_2]$). Hydrogen cyanide and cyanide ion combined are commonly termed free cyanide. The environmental fate of these cyanide compounds varies widely (Callahan et al. 1979).

Oxidation, hydrolysis, and photolysis are the three predominant chemical processes that may cause loss of simple cyanides in aquatic media are. Cyanides are oxidized to isocyanates by strong oxidizing agents; the isocyanates may be further hydrolyzed to ammonia and carbon dioxide (Towill et al. 1978). However, it has not yet been determined whether such oxidation and subsequent hydrolysis of isocyanate is a significant fate process in natural waters known to contain peroxy radicals (EPA 1992f).

In water, hydrogen cyanide and cyanide ion exist in equilibrium with their relative concentrations primarily dependent on pH and temperature. At pH <8, >93% of the free cyanide in water will exist as undissociated hydrogen cyanide (Towill et al. 1978). Hydrogen cyanide is hydrolyzed to formamide which is subsequently hydrolyzed to ammonium and formate ions (Callahan et al. 1979). However, the relatively slow rates of hydrolysis reported for hydrogen cyanide in acidic solution (Kreible and McNally 1929; Kreible and Peiker 1933) and of cyanides under alkaline conditions (Wiegand and Tremelling 1972) indicate that hydrolysis is not competitive with volatilization and biodegradation for removal of free cyanide from ambient waters (Callahan et al. 1979).

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The alkali metal cyanides are very soluble in water. As a result, they readily dissociate into their respective anions and cations when released into water. Depending on the pH of the water, the resulting cyanide ion may then form hydrogen cyanide or react with various metals in natural water. The proportion of hydrogen cyanide formed from soluble cyanides increases as the water pH decreases. At pH <7, >99% of the cyanide ions in water is converted to hydrogen cyanide (Towill et al. 1978). As the pH increases, cyanide ions in the water may form complex metallocyanides in the presence of excess cyanides; however, if metals are prevalent, simple metal cyanides are formed. Unlike water-soluble alkali metal cyanides, insoluble metal cyanides such as are not expected to degrade to hydrogen cyanide (Callahan et al. 1979).

The significance of photolysis in the fate of cyanides in water has not been fully investigated. Hydrogen cyanide and cyanide ions in aqueous solution have been found to be very resistant to photolysis by natural sunlight, except under heterogeneous photocatalytic conditions (Callahan et al. 1979; Frank and Bard 1977). Photocatalytic oxidation may not be significant in natural waters, however, because of significant light reduction at increasingly greater depths (EPA 1992f). In clear water or at water surfaces, some metallocyanides, such as ferrocyanides and ferricyanides, may decompose to the cyanide ion by photodissociation and subsequently form hydrogen cyanide. Because of adsorption of ferrocyanide onto soil surfaces and sediment of surface waters, and light scattering in turbid waters in the field, the rate of free cyanide formation from the photolysis of ferrocyanide in runoff and surface water from wash out of ferrocyanide in de-icing salt will be slower than from laboratory photolysis with clean water (Callahan et al. 1979).

Biodegradation is an important transformation process for cyanide in natural surface waters, and is dependent on such factors as cyanide concentrations, pH, temperature, availability of nutrients, and acclimation of microbes. However, additional data are needed to assess the relative significance of this process in determining the fate of aquatic cyanides (Callahan et al. 1979). Although cyanide is toxic to microorganisms at concentrations as low as 5-10 mg/L (Klecka et al. 1985; Malaney et al. 1959), acclimation increases tolerance to this compound (Raef et al. 1977a). A number of pure cultures of microorganisms degrade low concentrations of cyanide under both aerobic and anaerobic conditions (Callahan et al. 1979; EPA 1992f; Towill et al. 1978). However, biodegradation data derived from use of a pure culture are not strictly relevant to natural waters which contain mixed cultures. Mixed microorganisms in sewage sludge or activated sludge acclimated to cyanide also significantly biodegrade concentrations ≤ 100 mg/L of most simple and complex cyanides (Gaudy et al. 1982; Pettet and Mills 1954; Richards and Shieh 1989; Shivaraman et al. 1985). In a study to evaluate the effect of cyanide on biochemical oxidation conducted in sealed vessels, a 50% loss of cyanide at concentrations ≤6 mg/L in

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2 natural river waters occurred at times estimated to range from <10 to 24 days (Ludzack et al. 1951). The rate of loss appeared to be linear with time. These data may represent a biodegradation half-life; however, the possibility of loss by chemical reaction was not addressed in this study.

Most of the available information on the mechanisms of biodegradation of cyanides in water comes from studies to evaluate this process as a means of detoxication of cyanide-containing wastes. Raybuck (1992) has recently reviewed the role of microbes in cyanide degradation and has categorized the microbial enzymes which use cyanide as a substrate according to the following types of reactions: substitution/addition, hydrolysis, oxidation, and reduction. Sulfur transferases such as rhodanese are involved in substitution reactions which result in the conversion of cyanide to the less toxic thiocyanate; whereas, pyridoxal phosphate enzymes are involved in substitution/addition reactions which result in production of nitrile derivatives of α-amino acids. These organic nitriles may then be ultimately degraded via enzyme catalyzed hydrolysis to either the corresponding amino acid and ammonia (without formation of the free amide), or to the carboxylic acid and ammonia (via formation of the free amide). The cyanide hydratase and cyanidase enzymes catalyze the hydrolysis of cyanide to formamide or formic acid and ammonia, respectively. A strain of *Alcaligenes xylosoxidans subsp. denitrifcans* has been found to effectively hydrolyze cyanide concentrations up to 300 mg/L down to very low levels (0.01-0.02 mg/L) and to be resistant to inactivation by chloride, sulfate, iodide, Fe^{+2}, Zn^{+2}, or Ni^{+2} at concentrations of 70 mg/L (Basheer et al. 1992). Thus, these hydrolytic systems are some of the most promising for detoxification of cyanide containing waste waters (Raybuck 1992). Few microbial systems have been identified that are capable of direct oxidation or reduction of cyanide. *Bacillus pumulus, Pseudomonas fluorescens,* and *Pseudomonas paucimobili* have all been found to oxidize cyanide to ammonia and carbon dioxide (Meyers et al. 1993). Cyanic acid has been postulated to be an intermediate in the aerobic oxidation of cyanide by *P. jhorescens).* In an aerobic batch bioreactor experiment, *Pseudomonas putida* was found to significantly degrade 4 mM sodium cyanide (cyanide concentration approximately 100 mg/L) to ammonia and carbon dioxide (Chapatwala et al. 1993). Other evidence indicates that formamide and formate are additional transformation products in microbial oxidation of cyanide by this species, inferring that there may be more than one pathway of cyanide biotransformation involved (Kunz et al. 1992; White et al. 1988). Several bacterial species have been identified recently that are capable of oxidative degradation of metallocyanides (Silva-Avalos et al. 1990). The cyanide oxygenase system involved in this process offers a new technology for the treatment of metal cyanide wastes (Raybuck 1992).

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The ferrocyanide complex is not easily biodegradable (Belly and Goodhue 1976; Pettet and Mills 1954). However, when an aqueous solution of potassium ferrocyanide was seeded with pure culture of *Pseudomona aeruginosa, E. coli,* or a mixture of the two bacteria, formation of free cyanide was observed after a delay period of ≈ 2 days (Cherryholmes et al. 1985). The rate of free cyanide formation increased with addition of nutrient in water, and a free cyanide concentration $\leq 4,000$ μg/L was detected at the end of 25 days. It was shown that the free cyanide formation was due to biodegradation and not to either photolysis or hydrolysis. The relevance of this study to the fate of ferrocyanide complexes in natural water or industrial effluents is difficult to assess because cyanide concentrations used in these experiments (3,300 mg/L) are rarely encountered in these media.

Biodegradation is also a significant transformation process for thiocyanates in natural waters; however, additional data are needed to assess the relative importance of this process. Like cyanide, thiocyanate is toxic to microorganisms at high concentrations and acclimated cultures have increased tolerance to this compound (Boucabeille et al. 1994a). Laboratory studies have shown that at concentrations up to at least 1.42 g/L, thiocyanate was completely degraded within 4 days to ammonia and sulfate ion ($So_4^=$) by an acclimatized co-culture of two bacteria *(Acinetobacter johnsonii* and *Pseudomonas diminuta)* isolated from sludge from an urban sewage treatment plant (Boucabeille et al. 1994a). Thiosulfate ion ($S_2O_3^=$) was identified as the intermediate in this degradation pathway.

Several studies document the biodegradation of mixtures of cyanides and thiocyanate in waste waters (e.g., Boucabeille et al. 1994b; Mudder and Whitlock 1984; Paruchuri et al. 1990; Shivaraman et al. 1985). Under aerobic conditions, the biodegradation of cyanides and thiocyanate initially produces ammonia, which is converted to nitrite and nitrate in the presence of nitrifying bacteria; whereas anaerobic biodegradation under denitrification conditions may produce nitrogen (Richards and Shieh 1989). Complete biodegradation of simple and metal complexed cyanides and thiocyanate from mining waste waters by various *Pseudomonas, Vibrionacas,* and *Enterobacterias* has recently been reported (Boucabeille et al. 1994b). Biodegradation of cyanide and thiocyanate resulted in the formation of ammonia, with or without accumulation of nitrite and/or nitrate, depending on whether a batch, fed-batch, or continuous treatment process was used. Sulphate ions were produced from thiocyanate degradation. Shivaraman et al. (1985) reported the uninhibited microbial degradation of thiocyanate and cyanide to ammonia by acclimatized mixed cultures at cyanide concentrations up to 22.40 ± 1.34 mg/L; whereas, Paruchuri et al. (1990) have reported the complete inhibition of microbial degradation of thiocyanate in the presence of 10 mg/L cyanide.

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Cyanogen reacts slowly with water to produce hydrogen cyanide, cyanic acid, and other compounds (Callahan et al. 1979). No information could be found in the available literature on the transformation of cyanogen chloride in water; however, volatilization would be expected to be the predominant fate process for both cyanogen chloride and cyanogen in water.

5.3.2.3 Sediment and Soil

Analogous to the fate of cyanides in water, it is predicted that the fate of cyanides in soil would be dependent on cyanide concentrations, pH, temperature, metal content, concentration of microbes, availability of nutrients, and acclimation of microbes. Cyanide may occur as hydrogen cyanide, alkali metal salts, or as immobile metallocyanide complexes. In soil, cyanide present at low concentrations would biodegrade under aerobic conditions with the initial formation of ammonia, which will be converted to nitrite and nitrate in the presence of nitrifying bacteria. Under anaerobic conditions, cyanides will denitrify to gaseous nitrogen (Richards and Shieh 1989). Upper limits of 200 and 2 ppm (mg/kg CN⁻), respectively, have been reported for uninhibited aerobic and anaerobic biodegradation of cyanide in soil (Fueller 1984); however, these limits have not been confirmed in other studies (Thomas and Lester 1993). Cyanide ions in soil are not involved in oxidation-reduction reactions but may undergo complexation reactions with metal ions in soil (Towill et al. 1978).

No information could be found in the available literature on the transformation of cyanogen or cyanogen chloride in soil or sediment; however, because these compounds are highly volatile gases, biotic or abiotic degradation would not be expected to be significant fate processes compared to volatilization.

The fate of thiocyanate in soil is largely uncharacterized. Early studies have shown that thiocyanate can undergo both aerobic (Betts et al. 1979) and anaerobic microbial degradation (Betts et al. 1979; Stafford and Callely 1969; Youatt 1954); however, the degradation pathway has not been defined (Brown and Morra 1993). Saturated soils treated with thiocyanate were found to emit carbonyl sulfide (COS) (Minami 1982; Minami and Fukushi 1981). Katayama et al. (1992, 1993) have reported the formation of carbonyl sulfide from the biodegradation of thiocyanate by pure and mixed cultures of *Thiobacillus thioparus.* These species are ubiquitous in soil (Kelly and Harrison 1989). In a recent laboratory investigation of the fate of ionic thiocyanate in six different soils, Brown and Morra (1993) concluded that microbial degradation is the primary mechanism for thiocyanate disappearance at or below 30 °C, with carbonyl sulfide proposed as a possible hydrolysis product. Loss of thiocyanate at higher temperatures (50-60 °C) did not appear to result from microbial degradation; the observed decreases in thiocyanate concentrations

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of soil extracts with incubation time at elevated temperatures were postulated to result primarily from increased sorption or increased sorption kinetics, but abiotic catalysis of thiocyanate degradation was also noted as a possible cause.

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

The values reported for environmental levels of cyanide and thiocyanate must be interpreted with caution. Methods for the analysis of cyanide and thiocyanate have many interferences. In addition, samples containing cyanide and/or thiocyanate may not be stable if the samples are not carefully preserved. It should be noted that the amounts of cyanide or thiocyanate found by chemical analysis are not necessarily the amounts that are bioavailable.

Reliable evaluation of the potential for human exposure to cyanide depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. In reviewing data on cyanide levels monitored in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable.

5.4.1 Air

The concentration of hydrogen cyanide in the northern hemisphere's non-urban troposphere ranges from 160 to 166 ppt (Cicerone and Zellner 1983; Jaramillo et al. 1989). Although ambient monitoring data regarding cyanide in air near source areas (e.g., hydrogen cyanide manufacturing industries, coke production industries, waste disposal sites) were not located in the available literature, the hydrogen cyanide concentration in the vicinity of the source areas would be expected to be higher than the nonurban tropospheric concentration. The semiquantitatively measured hydrogen cyanide concentrations in the offgas from shale oil retorting processes ranged from 6 to 39 ppm in one retort at one site; however, hydrogen cyanide was not detected in retorts at another site (Sklarew and Hayes 1984).

No information could be found in the available literature on concentrations of cyanogen, cyanogen chloride, or thiocyanates in air.

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5.4.2 Water

Cyanide has been detected in waste waters from plating industries at concentrations up to 100,000 mg/L (Chen et al. 1994; Grosse 1986); from a textile industry at a maximum concentration of 0.2 mg/L (Rawlings and Samfield 1979); in the primary and secondary effluents from a Los Angeles City waste water treatment plant at mean concentrations of 29 ± 4 and 10 ± 6 μg/L (0.03 and 0.01 mg/L), respectively (Young 1978); and in the final effluent from a Los Angeles County waste water treatment plant at a mean concentration of 240 μg/L (0.24 mg/L) (Young 1978). Waste waters from a mining site storage basin were found to contain cyanide at concentrations of >l0 mg/L as simple cyanides; 20-80 mg/L as combined simple cyanides and copper(I) cyanide; 20-190 mg/L as combined simple cyanides, copper(I) cyanide, and ferrocyanide; and 300-450 mg/L as thiocyanate (Boucabeille et al. 1994b). Waste waters from gold mines have been reported to contain total cyanide and thiocyanate concentrations ranging from 0.5 to 10 mg/L and 45 to 75 mg/L, respectively (Mudder and Whitlock 1984). Weak acid dissociable (WAD) cyanide was measured in tailing ponds at several Nevada gold mines in 1990; the concentrations ranged from 8.4 to 216 mg/L at the discharge pipe and from 7.8 to 11.3 mg/L at the reclaim area (Henny et al. 1994). In New York state alone, 47 industries discharged 3,877 pounds of cyanide into streams in 1982 (Rohmann et al. 1985). Cyanide has also been found in groundwater below landfills and disposal sites (Anonymous 1990; Myers 1983; Venkataramani et al. 1984). A maximum cyanide concentration of 1,200 μg/L (1.2 mg/L) was found in shallow groundwater ≤ 3 meters below an inactive drum recycling facility in Miami, Florida (Myers 1983). Cyanide concentrations were found to range from 0.005 to 14.0 mg/L in the leachates from 14 of 43 U.S. landfills with industrial wastes; the "typical" cyanide concentration was reported to be 0.008 mg/L (Venkataramani et al. 1984). Data from the Nationwide Urban Runoff Program as of 1982 indicate that cyanide was found in urban runoff samples collected in 4 of 15 urban areas across the United States: Denver, Colorado; Long Island, New York; Austin Texas; and Bellevue, Washington. Overall, cyanide was detected in 16% of the urban runoff samples collected, at concentrations ranging from 2 to 33 μg/L (Cole et al. 1984).

Based on data obtained from the EPA STORET database, the mean cyanide concentration in most surface waters tested in the United States is not >3.5 μg/L (Fiksel et al. 1981); however, 37 of 50 states (74%) have locales where cyanide concentrations in ambient water are >3.5 μg/L. Areas with levels >200 μg/L include portions of southern California, North Dakota, South Dakota, Iowa, northwest Georgia, western New York, and western Pennsylvania (Fiksel et al. 1981). It should be noted that these results are applicable only to the period from the late 1970s to the early 1980s. Furthermore, the reliability of some of these early STORET data may be questionable. Analyses of more recent STORET cyanide data could not be found.

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Cyanide at a concentration >l µg/L was detected in water from the Great Lakes (Great Lakes Water Quality Board 1983). The concentration of cyanide in 104 samples collected during 1980 and 1981 at various points on the Ohio River and its tributaries was reported to range from <5 to 80 µg/L (Ohio River Valley Sanitation Commission 1982). The highest concentration was detected in water from Beaver Falls, Pennsylvania.

Cyanogen chloride is formed in drinking water due to reaction of humic substances with chloramine formed during chlorination (Ohya and Kanno 1987). It has been reported that the concentration of cyanogen chloride in drinking water is most influenced by the final disinfectant. The use of chloramine as a final disinfectant produces levels of cyanogen chloride that are 4-15 times higher than levels produced when chlorine is used (Jacangelo et al. 1989; Krasner et al. 1989). Cyanogen chloride was qualitatively detected during a 1975 survey of Cincinnati, Ohio drinking water (Kopfler et al. 1977). A lo-city survey that was conducted as part of the 1974 EPA National Organics Reconnaissance Survey revealed that cyanogen chloride was present in 8 of 10 drinking water supplies analyzed (no quantitative concentration values given) (Bedding et al. 1982). In a 1988 survey of 35 water utilities, the quarterly median cyanogen chloride concentrations in drinking water ranged from 0.45 to 0.80 µ/L (Krasner et al. 1989).

No information could be found in the available literature on the levels of thiocyanate in ground, surface, or drinking water. Thiocyanate is found in concentrations ranging from 100 to 1,500 mg/L in coal plant waste waters (Ganczarczyk 1979; Jensen and Tuan 1993), and from 300 to 450 mg/L in mining (gold extraction) waste waters (Boucabeille et al. 1994b).

5.4.3 Sediment and Soil

No information could be found in the available literature on concentrations of cyanides, cyanogen, or cyanogen chloride in soil or sediments. The highly volatile gases hydrogen cyanide, cyanogen, and cyanogen chloride (see Table 3-2) would not be expected to be present in sediment or soil in any appreciable amounts.

Monitoring data on thiocyanate concentrations in soils are scarce. Concentrations of thiocyanate in soils amended with defatted seed meal of *Brassicu napus L.* (rapeseed) were reported to be on the order of 6 µg/g (Brown et al. 1991). No information could be found in the available literature on thiocyanate concentrations in sediments.

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5.4.4 Other Environmental Media

The primary cyanide source in food is cyanogenic glycosides. Plants containing cyanogenic glycosides can produce hydrogen cyanide by acid hydrolysis or by the action of the enzyme β-glucosidase (EPA 1980a; Fiksel et al. 198 1; Seigler 199 1). Hydrogen cyanide release can occur either during maceration, which activates the intracellular β-glucosidase, or in the gut by the action of β-glucosidase produced by microflora. The level of activity of β-glucosidase in the gut depends on the bacterial composition and the pH level (WHO 1992). There are approximately 60 known cyanogenic glycosides, all of which differ considerably in bioavailability (Seigler 1991). Those cyanogenic glycosides that are absorbed intact from the gut are not metabolized to hydrogen cyanide by mammalian enzymes. The potential toxicity of cyanogenic plants depends on their ability to release hydrogen cyanide during preparation or digestion at concentrations high enough to be of concern for human health (WHO 1992).

Over 2,650 plant species can produce hydrogen cyanide (Seigler 1991; Swain et al. 1992). These include edible plants such as almonds, pits from stone fruits (e.g., apricots, peaches, plums, cherries), sorghum, cassava, soybeans, spinach, lima beans, sweet potatoes, maize, millet, sugarcane, and bamboo shoots (Fiksel et al. 198 1). The cyanogenic glycoside content of a foodstuff is usually expressed as the amount of cyanide released by acid hydrolysis; glycoside concentrations are rarely reported (WHO 1992).

Cyanide levels measured in some foods are as follows: cereal grains and their products, 0.001-0.45 μg/g; soy protein products, 0.07-0.3 μg/g; and lima beans, 0.1-3 mg/g (Honig et al. 1983; Towill et al. 1978). The cyanide equivalent of total cyanogenic content (i.e., cyanogenic glycosides, cyanohydrins, and hydrogen cyanide) of cassava root has been reported to range from 91 to 1,515 mg/kg hydrogen cyanide (86-1,458 μg/g CN$^-$) dry weight (d/w) (O'Brien et al. 1992). Cassava is the major starchy food for more than 300 million people in many tropical countries of the world, and many cultivars are toxic (Seigler 1991). Effective processing can reduce the amount of total cyanogens in fresh cassava roots to significantly lower levels in foods ready for consumption (Mlingi et al. 1993; O'Brien et al. 1992). For example, the mean cyanide content in garri (a flour product of grated, pressed, and fermented cassava root pulp) from a city market in Nigeria ranged from 10.6 to 22.1 μg/g d/w (Ukhun and Dibie 1989). A somewhat wider distribution of results was obtained in another recent evaluation of commercial garri from three main garri-producing Nigerian communities (Aletor 1993). The mean total cyanide content (glucosidic plus non-glucosidic)of 38.8% of all samples (n = 108) ranged from 0 to 10 mg/kg hydrogen cyanide (0-9.6 μg/g CN-); whereas, 40.7, 12.9, and 7.4% of the samples had mean total cyanide contents of 10-20,20-30, and 3040 mg/kg hydrogen cyanide (9.6-l 9, 19-29, and 29-39 μg/g CN$^-$), respectively.

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The mean cyanide content of domestic samples of "sweet" to "bitter" cassava food products in Camaroon was reported to range from 18.6 to 94.9 mg/kg hydrogen cyanide (17.9-91.4 µ/g CN-) d/w for a dried cassava flour, and from 0.0 to 0.9 mg/kg hydrogen cyanide (0.0-0.9 µg/g CN-) d/w for a cassava paste (O'Brien et al. 1992). Improper processing of cassava roots may result in maintenance of cyanogenic content of cassava food products at levels which are toxic (Mlingi et al. 1992, 1993; O'Brien et al. 1992). Cassava is a starch staple, but it is low in protein (Gomez et al. 1988). Low protein intake results in a decrease in available sulfur for conversion of cyanide to thiocyanate (Mlingi et al. 1993; Tylleskar et al. 1992). Hydrogen cyanide concentrations in sorghum leaves have been reported to range from approximately 200-l ,300 ppm (192-l ,250 µg/g CN-) wet weight (w/w), with higher concentrations observed in early growth stages and at lower levels of phosphorus fertilization (Chand et al. 1992).

In apricot pits, the cyanide concentration may vary from 8.9 to 217 mg/100 g (89-2,170 µg/g) w/w, depending on the type of cultivar, season, and geographic area (Lasch and El Shawa 1981). Swain et al. (1992) reported a mean cyanide concentration in black cherry *(Prunus serotina Ehrh.)* fruits somewhat greater than 3 µmol/seed at maturity, which is equivalent to.a mean cyanide content of 78 µg/seed; insufficient information was provided to allow conversion of these results to weight per weight (w:w) units. In a recent laboratory study, Voldrich and Kyzlink (1992) reported *cyanide concentrations in* canned unpitted fruits (peaches, apricots, plums, and cherries) ranging from 0 to 4 mg/kg µg/g) w/w, depending on the glycoside content of the raw fruits and the conditions of heat processing. These authors noted that the observed cyanide levels were not negligible relative to an allowable daily intake (ADI) value for cyanide of 0.05 mg/kg body weight. An adult (70 kg body weight) could consume approximately 1 kg of canned fruits with a cyanide content of 4 mg/kg without exceeding this AD1 value; however, a safe portion for a child (15 kg body weight) would be only about 180 grams. The analysis of 233 samples of commercially available and homemade stone-fruit juices showed that pitted fruit juices had lower cyanide concentrations than unpitted or partially pitted fruit juices, indicating that the pits are the primary sources of cyanides in these juices (Stadelmann 1976). For example, the hydrogen cyanide content of a home-made mixed cherry juice from pitted fruits was 5.3 mg/L, compared to 23.5 mgk in a cherry juice containing 100% crushed pits. This study also reported the following levels (median concentrations in mg/L) of hydrogen cyanide in commercial fruit juices: cherry, 4.6; apricot, 2.2; prune, 1.9; and peach, 2.9. Stadelmann (1976) recommended that the maximum hydrogen cyanide content allowed in fruit juices should be set at a level of 5 mg/L.

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Cyanide can also be present in foodstuffs as residues from cyanide fumigation (Fiksel et al. 1981). Human exposure to naturally occurring cyanide in foods in the United States is expected to be low compared to certain populations in the Third World who subsist on cassava and similar crops (Fiksel et al. 1981).

Edible plants such as kale, cabbage, radishes, broccoli, brussels sprouts, cauliflower, collards, mustard greens, turnips, and kohlrabi contain glucosinolates which are hydrolysed by the endogenous enzyme myrosinase to produce toxic products, including thiocyanate (Abukutsa et al. 1993; Bible and Chong 1975; Bible et al. 1980; Carlson et al. 1985, 1987; Olea and Parras 1992; Olea-Serano et al. 1988). Vegetables from the Brussica family (e.g., cabbages, kohlrabi, kale) contain high levels of thiocyanate ranging from 5 to 660 µg/g w/w (Weuffen et al. 1984). Kale leaves have been reported to contain concentrations of potassium thiocyanate at harvest ranging from 447 to 5,067 ppm µg/g) d/w (equivalent to thiocyanate concentration of 267-3,035 µg/g d/w) depending on the fertilizer nitrogen source (Abukutsa et al. 1993). Other commonly consumed vegetables (e.g., lettuce, spinach, radishes) have been found to contain thiocyanate at concentrations ranging from approximately 0.1-5.0 µg/g w/w, with concentrations usually <2.0 µg/g w/w (Weuffen et al. 1984). Milk and other dairy products have been reported to contain thiocyanate at concentrations ranging from cl to 9.0 µg/g; whereas concentrations in meat products have been reported to range from only 0.5 to 0.7 µg/g (Weuffen et al. 1984).

Laetrile (amygdalin), a drug formerly used in clinical trials for the treatment of cancer (Khandekar and Edelman 1979); sodium nitroprusside, a drug used to reduce high blood pressure (Aitken et al. 1977; Vesey et al. 1976); and a series of commercially important, simple, aliphatic nitriles (e.g., acetonitrile, propionitrile, acrylonitrile, n-butyronitrile, maleonitrile, succinonitrile) (Willhite and Smith 198 1) release cyanide upon metabolism. These drugs and industrial chemicals have been associated with human exposure to cyanide and have caused serious poisoning and, in some cases, death.

Reported levels of cyanide in tobacco smoke are quite variable. Cyanide levels in mainstream (inhaled) smoke from U.S. commercial cigarettes have been reported to range from 10 to 400 ug per cigarette, with the ratio of cyanide concentration in sidestream smoke to mainstream smoke ranging from 0.006 to 0.27 (Fiksel et al. 1981). In studies which have included non-U.S. commercial cigarettes, hydrogen cyanide concentrations in mainstream and sidestream smoke ranging from 280 to 550 µg/cigarette and 53 to 111 µg/cigarette, respectively, have been reported; sidestreammainstream ratios of hydrogen cyanide concentrations ranged from 0.06 to 0.50 (Baker and Proctor 1990; Guerin et al. 1987).

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Cyanides have been detected in automobile exhaust. The average emission rate was 11-14 mg/mile for cars not equipped with catalytic converters and 1 mg/mile for cars with catalytic converters operating under optimum conditions. Cars with malfunctioning catalytic converters may emit as much or more hydrogen cyanide than cars without such equipment (Fiksel et al. 1981).

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

The general population may be exposed to cyanide from inhaling air and ingesting food and drinking water contaminated with it. Since most of the cyanide in the air will be present as hydrogen cyanide (see Section 5.3.2.1), the primary inhalation exposure to cyanide will occur from hydrogen cyanide. The concentration of hydrogen cyanide in the air of non-urban areas is $\approx$ 160-166 ppt (see Section 5.4.1). Based on an atmospheric hydrogen cyanide concentration of 170 ppt (188 ng/m^3) and an average daily inhalation volume of 20 m^3, the inhalation exposure of the general U.S. non-urban, nonsmoking population to hydrogen cyanide is estimated to be 3.8 µg/day. In drinking water, cyanide may be present as cyanogen chloride (see Section 5.4.2). In 1988, the quarterly median cyanogen chloride concentration in drinking water from 35 U.S. water utilities ranged from 0.45 to 0.8 µg/L (0.19 to 0.3 µg/L cyanide) (Krasner et al. 1989). Based on *a* daily drinking water consumption of 2 L for a 70-kg adult, the daily intake of cyanogen chloride is estimated to be 0.9-l .6 µg, which is equivalent to 0.4-0.7 µg of hydrogen cyanide. EPA has established a maximum concentration level (MCL) of 0.2 mg/L for cyanide in drinking water (see Chapter 7), which is equivalent to a daily intake of 0.4 mg, based on a daily drinking water consumption rate of 2 L for a 70-kg adult (EPA 1991a). Estimates of the cyanide concentration in the total diet of a U.S. adult were not located in the available literature. Therefore, no estimate of daily cyanide intake from food can be made. In the United States, human exposure to cyanide from foods in which it occurs naturally is expected to be low, but is likely to exceed cyanide intake from inhalation of air and ingestion of drinking water (Fiksel et al. 1981). The EPA has established tolerances for hydrogen cyanide and calcium cyanide in various foods ranging from 25 to 250 ppm (EPA 1971b, 1971c, 1975b) and from 5 to 25 ppm (EPA 1971a), respectively (see Chapter 7). Poitrast et al. (1988) have estimated an overall allowable daily intake of 0.6 mg for cyanide, incorporating a safety factor of l00-1,000 to ensure that the potential for an infant receiving a toxic dose of cyanide from breast milk is quite low.

The dietary cyanide intake of Tukanoan Indians in northwest Amazonia who rely heavily on high (>70% of all foods) cyanide-containing varieties of cassava was estimated to be >20 mg/day (Dufour 1988). The cassava processing techniques of the Tukanoans are very sophisticated and very effective in reducing the cyanide concentration in the crop. The author did not find physical disorders in Tukanoan Indians

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attributable to high cassava diets, in contrast to observations about cassava-consuming populations in Africa. Also, the variety of cassava may differ between geographical areas, which may account for the observed differences in toxicity among different populations (Rosling 1988). However, in some African populations, outbreaks of acute cyanide intoxications have been found to result from incomplete processing of cassava, resulting in highly elevated cyanide levels in combination with chronic dietary protein malnutrition. This occurred when, due to a food shortage, the lengthy sun drying normally used to remove cyanogenic glucosides was replaced by repeated pounding and drying to obtain flour for consumption in one day (Mlingi et al. 1992, 1993; Tylleskar et al. 1992).

The primary route of exposure to thiocyanates for the general population appears to be from ingestion of foods in which thiocyanate occurs naturally (e.g., cabbage, kale, spinach, kohlrabi). Estimates of the thiocyanate concentration in the total diet of an adult in the United States were not located in the available literature; however, these would be expected to be quite low. Exposure to cyanide also is a source of thiocyanate exposure because thiocyanate is a major metabolite of cyanide in the human body.

Occupational exposures to cyanide are expected to occur primarily through inhalation and, less frequently, through skin absorption. Preliminary data from the NOES conducted by NIOSH from 1980-83 estimated that the number of workers potentially exposed to cyanide compounds in the United States from 198 1 to 1983 are as follows (NIOSH 1989a): cyanide, 367; hydrogen cyanide, 4,005; sodium cyanide, 66,493; potassium cyanide, 64,244; potassium silver cyanide, 3,215; calcium cyanide, 3,606; copper(I) cyanide, 22,339; ammonium thiocyanate, 90,599; cyanogen chloride, 1,393. Thiocyanate and cyanogen were not included in the NOES (NIOSH 1989a). These numbers do not include workers potentially exposed to trade-name compounds that contain cyanides or thiocyanates. Workers in various occupations may be exposed to cyanide compounds. People possibly exposed to cyanide include workers involved in electroplating, metallurgy, cyanotype printing, pesticide application, firefighting, steel manufacturing, and gas works operations; workers involved in the manufacture of cyanides, adiponitrile and other simple, aliphatic nitriles, methyl methacrylate, cyanuric acid, dyes, pharmaceuticals, or chelating agents; and people who work in tanneries, blacksmithing, metal cleaning, and photoengraving or photography industries (Fiksel et al. 1981; Lucas 1992; Willhite and Smith 1981). Workers in the oil shale retorting industry may be exposed to cyanide because the offgas from the retorting process contains hydrogen cyanide (see Section 5.2.1). Medical and emergency personnel (e.g., police and firefighters) who may be involved in resuscitation efforts or removal of gastric contents of postmortem victims of cyanide poisoning are potentially exposed to higher levels of cyanide (Andrews et al. 1989). The manufacture of industrial inorganic chemicals may be a significant potential source of occupational exposure to cyanogen

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chloride (NIOSH 1989a). Potential sources of occupational exposure to ammonium thiocyanate include the manufacture of electronic computing equipment, research and development laboratories, newspaper and other commercial printing, general medical and surgical hospitals, production of adhesives and sealants, and the construction and furniture industries (NIOSH 1989a).

In a survey of the plating facility of a national airline conducted by NIOSH in December 1981, the concentrations of hydrogen cyanide in 3 work areas ranged from 0.001 to 0.004 mg/m^3 (0.0009 to 0.004 ppm) (NIOSH 1982). The cyanide concentrations in 4 work areas in a plating facility of an electrical and electronic company in Waynesboro, Virginia, ranged from 0.07 mg/m^3 (0.07 ppm hydrogen cyanide) in a salt pot room to 4.3 mg/m^3 (4.0 ppm hydrogen cyanide) beside a stripping tank (NIOSH 1976). Similarly, the concentration of cyanide in the breathing zone air of workers in a plating facility in Galion, Ohio, was 1.7 mg/m^3 (1.6 ppm hydrogen cyanide) (NIOSH 1978). In a recent NIOSH survey of a university art department foundry, hydrogen cyanide was detected in the smoke produced during pouring and knockout of castings at a concentration of approximately 4 ppm; hydrogen cyanide was not detected in personal breathing zone samples taken during knockout of castings (Lucas and Salisbury 1992). These levels are all below the NIOSH recommended ceiling limit of 4.7 ppm (NIOSH 1992).

Levels of cyanide and its metabolite thiocyanate in blood serum and plasma, urine, and saliva have been used as indicators of cyanide exposure in humans, particularly in workers at risk of occupational exposures, in smokers or nonsmokers exposed to sidestream or environmental tobacco smoke, in populations exposed to high dietary levels of cyanide, and in other populations with potentially high exposures (see Section 5.6). The correlation between increased cyanide exposure and urinary thiocyanate levels was demonstrated in workers exposed to 6.4-10.3 ppm cyanide in air (El Ghawabi et al. 1975). In another study, blood cyanide concentrations were found to vary from 0.54 to 28.4 μg/100 mL in workers exposed to approximately 0.2-0.8 ppm cyanide in air, and from 0.0 to 14.0 μg/100 mL in control workers (Chandra et al. 1988). Similar elevations in urinary thiocyanate levels were observed, with concentrations for exposed workers and controls ranging from 0.05 to 2.80 and 0.02 to 0.88 mg/mL, respectively.

The results of several studies which have shown elevated cyanide or thiocyanate concentrations in body fluids of smokers are summarized in Table 5-3. In general, these results indicate that serum cyanide levels (Cardeal et al. 1993; Symington et al. 1987) and plasma, serum, and saliva thiocyanate levels (Banerjee and Muthu 1994; Jarvis 1989; Maliszewski and Bass 1955; Pre and Vassy 1992, 1993; Waage et al. 1992; Yamanaka et al. 1991) could distinguish smokers from nonsmokers and/or light smokers. Pre and Vassy (1992) found that plasma thiocyanate was an indicator of smoking status that was not sensitive to light or

Table 5-3. Cyanide and Thiocyanate Concentrations (µg/mL)[a] in Smokers and Nonsmokers

Compound	Plasma		Serum		Saliva		Urine		Reference
	S[b]	NS[b]	S	NS	S	NS	S	NS	
Cyanide									
			2.11 (1.42–3.67)	0.78 (0.44–1.15)					Cardeal et al. 1993[c]
			6.8 (1.3–19.4)	2.9 (0.0–11.7)					Symington et al. 1987[c,d]
Thiocyanate									
			232 (10)	92 (9)					Banerjee and Muthu 1994[e]
	7.1	2.9			142	76	9.0	5.8	Jarvis 1989[f]
	7.1 (6.2–8.6)	2.0 (1.2–2.8)			75.7 (48.4–112.2)	20.3 (9.71–28.7)	12.3 (7.8–17.2)	2.1 (1.1–3.9)	Maliszewski and Bass 1955[c]
	8.7[g] (4.4–21.5) 3.3[i] (1.0–4.6)	1.8[h] (0.5–4.4)							Pré and Vassy 1992[e]
									Pré and Vassy 1993[e]
			6.6 (1.5) (<0.05–0.35)	1.2 (0.3) (<0.05–0.08)					Waage et al. 1992[e,j]
	2.1	3.7			88	33	18	19	Yamanaka et al. 1991[j,k]

a Values are means; values in parentheses are ranges or standard deviations.
b S = smoker; NS = nonsmoker
c No statistics reported
d As cited in Cardeal et al. 1993
e Results significantly different

f Results not significantly different
g Inhaling smokers
h Nonsmokers including passive smokers
i Noninhaling smokers
j Values estimated from graphical presentation of data
k All results, except urine, significantly different

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passive smoking. However, inhaling smokers were easily distinguished from noninhaling smokers. The authors concluded that a plasma thiocyanate concentration below 20 μmol/L (1,200 μg/L) indicated that passive smoking was very unlikely; whereas concentrations above 80-85 μmol/L (4,600-4,900 μg/L) were a reliable indication of active inhaling smoking. Yamanaka et al. (1991) found a correlation between the number of cigarettes smoked per day and the thiocyanate levels in plasma and saliva; however, in apparent contrast to results obtained by Maliszewski and Bass (1955), thiocyanate concentrations in urine of smokers and nonsmokers were not found to be significantly different. Chen et al. (1990) found that serum thiocyanate concentrations of 1 %month-old infants heavily exposed to environmental tobacco smoke (>20 cigarettes a day smoked in the home) were significantly higher than those of unexposed infants (p<0.05). Mean concentrations (± SD) in these respective groups were 36.2 ±14.88 μmol/L (2.1 f 0.9 μg/mL) and 27.7 ± 10.7 μmol/L (1.6 ± 0.6 μg/mL).

Positive correlations between fetal umbilical serum thiocyanate levels and serum thiocyanate levels of smoking mothers (Bottoms et al. 1982; Hauth et al. 1984) and mothers exposed to environmental tobacco smoke in the home (Bottoms et al. 1982) have been reported. Hauth et al. (1984) found that the mean serum thiocyanate concentration (95 μmol/L; 5.5 μg/mL) was significantly higher (p < 0.001) in smokers than in passive smokers (35.9 μmol/L; 2.1 μg/mL) or nonsmokers (32.3 μmol/L; 1.9 μg/mL). Similarly, the mean umbilical thiocyanate concentration in the newborn infants of smoking mothers (72 μmol/L; 4.8 μg/mL) was significantly higher than those in newborn infants of passive smokers (26 μmol/L; 1.5 μg/mL) and nonsmokers (23 μmol/L; 1.3 μg/mL). In contrast, Bottoms et al. (1982) found that among newborn infants of nonsmoking mothers, fetal umbilical thiocyanate concentrations increased with passive smoking in the home (p < 0.05).

Data on elevated levels of thiocyanate in body fluids resulting from consumption of cyanide-containing foods come primarily from populations in tropical regions which may consume large quantities of improperly processed cyanogenic plants such as cassava. Among four populations in Africa known to be exposed to high levels of dietary cyanide because of incomplete processing of cassava during drought periods, urinary thiocyanate concentrations (mean f SE) ranged from 350 f 39 to 1,120 f 75 μmol/L (20 ± 2-65 ± 4 mg/L), compared to urinary thiocyanate levels in the normal population of less than 100 μmoL (5.8 μg/L) (Mlingi et al. 1992, 1993; Tylleskar et al. 1992). The mean plasma thiocyanate concentration in one of these populations was 335 ± 12 μmol/L (19 ± 1 μg/L), compared to 28 f 4 μmol/L (1.6 ± 0.2 μg/L) in a control population (Mlingi et al. 1992). Elevated mean serum thiocyanate concentrations (11 ± 3 μg/L compared to reference values of 0.5-4 μg/L) were observed in only one of two populations in which this

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biomarker was measured (Tylleskar et al. 1992, 1994). There was no apparent explanation for this difference.

High serum thiocyanate concentrations (>180 pmol/L) have been found in Tukanoan Indians on traditional diets. However, the levels of residual cyanide appear to be tolerated well (Dufour 1988).

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Among the general population, subpopulations with the most likely potential for exposure to cyanide and thiocyanate include active and passive smokers (Fiksel et al. 198 1) and people who are exposed to house or other building fires (Andrews et al. 1989). Other subpopulations with potentially high cyanide or thiocyanate exposures are residents who live near industrial sites releasing cyanides or thiocyanates into the environment, residents who live near cyanide- or thiocyanate-containing hazardous waste sites, and people who consume foods high in cyanogenic glycosides. The fetuses of pregnant women who smoke or who are exposed to high levels of environmental smoke (i.e., passive smokers) may be subjected to potentially high exposures of cyanide and thiocyanate (Bottoms et al. 1982; EPA 1992f; Hauth et al. 1984). Workers involved in electroplating, metallurgy, pesticide application, firefighting, gas works operations, tanning, blacksmithing, metal cleaning, photoengraving, photography, cyanotype printing, the manufacture of steel, cyanides, adiponitrile and other nitriles, methyl methacrylate, cyanuric acid, dyes, pharmaceuticals, or chelating agents have the potential to be occupationally exposed to higher concentrations of cyanide than the general population (Fiksel et al. 1981; NIOSH 1989a). Workers in the following industries may also be exposed to higher concentrations of thiocyanate than the general population: manufacture of electronic computing equipment, research and development laboratories, newspaper and other commercial printing, general medical or surgical hospitals, production of adhesives and sealants, pesticide application, building and furniture construction, and handling, treatment or disposal of thiocyanate-containing wastes from industrial processes (Brown and Morra 1993; NIOSH 1989a). Two additional groups of people who may be at greater risk for cyanide exposure are those who are exposed to cyanide but are unable to smell the chemical (EPA 1987a) and patients with motor neuron disease (see Section 2.7).

Data related to the levels of cyanide or thiocyanate exposure in several of these population groups have been presented in Section 5.5. No data were found related to the levels of cyanide or thiocyanate exposure in cassava eaters in the United States. Also, no data were located in the available literature related to the levels of cyanide and thiocyanate exposure of people who live near industrial sites releasing cyanides or

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thiocyanates to the environment, or near hazardous waste sites. Cyanides (reported as cyanide, hydrogen cyanide, sodium cyanide, potassium cyanide, calcium cyanide, or copper (I) cyanide) have been detected in air, surface and groundwater, and soil samples at NPL hazardous waste sites; cyanogen and cyanogen chloride have been detected in soil samples at NPL hazardous waste sites; and thiocyanates have been detected in surface and groundwater, and soil samples at NPL sites (see Section 5.2) (HazDat 1996). There is a need for reliable data on the levels at which these substances are found in various media at these sites in order to estimate potential exposures of people living near hazardous waste sites.

5.7 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of cyanide is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of cyanide.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce or eliminate the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

5.7.1 Identification of Data Needs

Physical and Chemical Properties. As reported in Section 3.2, the relevant physical and chemical properties of cyanide compounds are known. Certain physical parameters such as octanol/water partition coefficient and soil partition coefficient that are used generally for covalently bound organic compounds to predict environmental fate and transport are neither available nor useful for most of the ionic cyanide compounds.

Production, Import/Export, Use, Release, and Disposal. Knowledge of a chemical's production volume is important because it may indicate the magnitude of environmental contamination and human exposure. Data regarding the production, trend, use pattern, and disposal of commercially significant

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cyanide compounds are available (CMR 1993; Curry 1992; Homan 1987; HSDB 1996; Sittig 1980; SRI 1994; TRI93 1995). It is known that the import and export of hydrogen cyanide is insignificant compared to its production; however, except for potassium cyanide, recent import and export data for other individual cyanide compounds are difficult to obtain (USDOC 1994). There are some less recent data regarding the release of cyanides in air (Fiksel et al. 1981; TRI88 1990) but, except for hydrogen cyanide (TR193 1995), more recent quantitative data regarding the release of cyanide compounds in air, water, and particularly soil and sediment are unavailable.

According to the Emergency Planning and Community Right-to-Know Act of 1986,42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. The Toxics Release Inventory (TRI), which contains this information for 1992, became available in May of 1994. This database will be updated yearly and should provide a list of industrial production facilities and emissions. Information in the TR193 (1995) data base pertains only to U.S. industrial facilities that manufacture or process hydrogen cyanide. There is a need for similar information on releases and off-site transfer from facilities that manufacture or process other cyanide compounds covered in this profile.

Cyanide is naturally present in many foods high in cyanogenic glycosides (Fiksel et al. 1981; Honig et al. 1983; Towill et al. 1978). No information was located in the available literature to indicate that cyanide enters foods during processing or that elevated cyanide concentrations are present in any consumer products. The two most likely sources of general population exposure to cyanide include people who inhale cigarette smoke (Fiksel et al. 1981) or individuals who are exposed to a house or other type of building fire (Andrews et al. 1989). There are EPA regulations regarding the disposal of cyanide wastes and OSHA and NIOSH regulations regarding the levels of hydrogen cyanide in workplaces (see Chapter 7). Additional research is needed on improved methods of pollution prevention and biodegradation to reduce or eliminate releases of cyanide compounds to the environment from industrial processes.

Environmental Fate. The environmental fate of hydrogen cyanide gas in air is well studied (Cicerone and Zellner 1983; Fritz et al. 1982); however, it would be useful if the role of particulate cyanides (e.g., sodium cyanide, potassium cyanide) in determining the fate of total cyanides in the air was known. Given that hydrogen cyanide occurs in the atmosphere from both natural and anthropogenic processes (Cicerone and Zellner 1983; Crutzen and Andreae 1990; Crutzen and Carmichael 1993; Fiksel et al. 1981; Knowles 1988; Lobert and Warnatz 1993), it would be useful if an estimate were available for the contribution of anthropogenic processes to the overall hydrogen cyanide burden in the atmosphere. It is generally known that volatilization and biodegradation will be important processes for the loss of cyanides in water

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(Callahan et al. 1979; Ludzack et al. 195 1; Raef et al. 1977a; Towill et al. 1978), but no experimental or estimated values for the half-life of cyanides in ambient water are available. No comprehensive data regarding the role of sorption in determining the fate of cyanides in water are available. It is generally known that volatilization from soil surfaces and biodegradation play significant roles in the loss of cyanides in soil (Towill et al. 1978), but no quantitative data regarding the half-life of cyanides in ambient soil are available. Additional data on the relative importance of volatilization and biodegradation in determining the fate of cyanides in soils are needed. The elucidation of the role of cyanide complexation by metals in soil and sediment in controlling the fate of cyanide would be useful.

Both cyanogen and cyanogen chloride are highly volatile gases, indicating that volatilization would be the major transport pathway for these compounds from surface water and soils. Cyanogen is highly reactive and does not persist in the environment unchanged (Towill et al. 1978). It also has been reported to react slowly with water to yield hydrogen cyanide and cyanic acid, among other products (Callahan et al. 1979), and this hydrolysis reaction may be a possible degradation pathway. Additional information on the environmental fate of cyanogen and cyanogen chloride is needed.

There is almost no available information on the environmental transport and partitioning of thiocyanate in the environment. At ambient temperatures, it appears that sorption and volatilization are not significant partitioning processes for thiocyanate in soil, with thiocyanate losses due primarily to microbial degradation (Brown and Morra 1993); however, additional research is needed in this area. Although biodegradation is a significant transformation process for thiocyanate in water, additional data are needed on the relative importance of this process in determining the fate of thiocyanates in natural water systems.

Bioavailability. Cyanide is known to be absorbed following inhalation, oral, and dermal contact (Gosselin et al. 1976; Rieders 1971). The environmental factors that may influence the bioavailability of cyanide from contaminated air, water, soil, or plant material have not been studied. Since cyanides are not strongly sorbed to soil and sediments (Callahan et al. 1979), the role of sorption may not be significant in determining the bioavailability of cyanides from different soils or waters. The bioavailability of cyanide from an environmental medium is expected to increase if the cyanide is present in water-soluble forms, such as ions or soluble complexes. The pH of a medium may also be significant in determining the bioavailability because hydrogen cyanide gas may be released as the pH of the medium decreases (Callahan et al. 1979; Towill et al. 1978). Data delineating the factors affecting the bioavailability of cyanide compounds from soil and other environmental media need further development, since the absorption studies discussed in Section 2.3.1 have been performed with the pure chemical.

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The factors that may influence the bioavailability of thiocyanate from various foods and other environmental media have not been investigated.

Food Chain Bioaccumulation. Simple cyanide compounds do not bioconcentrate in fish (ASTER 1994; Callahan et al. 1979; EPA 1985a). It would be useful to determine the bioconcentration potential for cyanide in fish from water dosed with less toxic and water-soluble cyanide complexes. There is no indication of biomagnification of cyanides in aquatic and terrestrial food chains. Because of the high toxicity of cyanides at high doses and rapid metabolism at low doses, biomagnification of cyanide in animals seems unlikely.

No information could be found in the available literature on the potential of thiocyanates for bioconcentration and food chain bioaccumulation.

Exposure Levels in Environmental Media. Data regarding the cyanide and thiocyanate levels in ambient air and drinking water are lacking; therefore, it is not possible to estimate exposure levels to cyanides from inhaling ambient air and ingesting drinking water. Although the cyanide and thiocyanate concentrations in certain foods are known (Abukutsa et al. 1993; Fiksel et al. 1981; Honig et al. 1983; Pre and Vassy 1992; Towill et al. 1978), neither the cyanide nor the thiocyanate content of a total diet sample consumed by an average adult is known; therefore, the dietary exposures of an average person to cyanide and thiocyanate are unknown. Reliable monitoring data for the levels of cyanide and thiocyanate in air, water, and total diet samples would be useful in estimating exposures from each source. Additional data on the levels of cyanide and thiocyanate in soils will also be useful. It will also be useful to develop data that would clearly establish whether cyanides or thiocyanates pose acute or chronic exposure hazards for residents in the vicinity of hazardous waste sites. This information should include data on background concentrations in all media.

Reliable monitoring data for the levels of cyanide and thiocyanate in contaminated media at hazardous waste sites are needed so that the information obtained on levels of cyanide and thiocyanate in the environment can be used in combination with the known body burdens of cyanide and thiocyanate to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites. Also, there is a need for data relating to exposure levels of cassava eaters in the United States.

Exposure Levels in Humans. The levels of cyanide and thiocyanate in various human tissues and body fluids of both control and occupationally exposed groups and of smokers and nonsmokers are

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available (see Sections 2.3.4, 2.6.1, and 5.5). The levels of these chemicals in humans consuming foods containing cyanogenic materials also are available.

Exposure Registries. No exposure registries for cyanide or thiocyanate were located. These compounds are not currently among the compounds for which a subregistry has been established in the National Exposure Registry. These compounds will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposures to these compounds.

5.7.2 Ongoing Studies

A search of the Federal Research in Progress database (FEDRIP 1994) indicates that the following research studies are in progress to fill in the data gaps discussed in Section 5.7.1.

The U.S. Bureau of Mines-Reno Research Center is conducting studies on the use of thiosulfate as an alternative to cyanide for refractory gold ores as a means of pollution prevention and on the fate of cyanide in solution after land application.

The U.S. Bureau of Mines-Twin Cities Research Center is conducting research on the development of novel hydrological and geochemical systems for in situ leach mining which includes development of a new noncyanic, nontoxic precious metals lixiviant which is a good candidate for in situ mining systems where groundwater contamination is of paramount concern.

The Department of Federal Affairs, Washington, D.C., is evaluating the use of gamma radiation as an energy source for the photolytic destruction of aqueous organic wastes, including cyanide.

The U.S. EPA is funding research at Ionedge Corporation, Fort Collins, Colorado, to develop a process for zinc-graphite and zinc-cadmium alloy dry plating as environmentally safer alternatives to cadmium electroplating in cyanide baths. Successful development of these technique could lead to a method which would potentially eliminate the environmental and occupational hazards associated with cadmium electroplating.

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The U.S. EPA is funding research at Emec Consultants, Export, Pennsylvania, on methods to the suppress or eliminate cyanide formation in spent potlining from industrial primary aluminum production cells. Because over 100,000 tons of this material are disposed in landfills annually, it would be desirable to avoid the formation of cyanide during the production of the cells.

The European Coal and Steel Community is funding research at Stoke Orchard, Cheltenham, Gloucestershire, to develop a catalyst for the conversion of ammonia and hydrogen cyanide in coal gasification and combustion gases to nitrogen at high temperatures. Successful completion of this research will provide methodology to eliminate release of hydrogen cyanide to the atmosphere from these processes.

The CSIRO Division of Mineral Products, Port Melbourne, Victoria, Australia, is conducting research to develop a process to recover fluoride and aluminum from spent pot lining ash with concurrent production of an environmentally safe residue that is suitable for disposal. The proposed method involves initial calcination which thermally decomposes the cyanide in the spent pot lining. Successful completion of this research would reduce the amount of hazardous wastes that contain potentially harmful leachable cyanides that can enter the groundwater during open air storage.

The National Science Foundation is funding research at the South Dakota School of Mines, Rapid City, South Dakota, to develop an alternative approach to the extraction of precious metals from refractory ores which will pose a much lesser threat to environmental quality than the presently predominant cyanide leaching process.

The U.S. Department of Energy is funding research at Allied-Signal, Inc., Kansas City, Missouri, which involves integrating advanced pollution prevention and waste minimization technologies into U.S. industry. One major area of technology integration is plating replacements for cyanide, hexavalent chromium, cadmium-containing compounds, and other heavy metals.

The U.S. Department of Energy is funding research at the Idaho National Engineering Laboratory, Idaho Falls, Idaho, to determine if sawdust can be used exclusively to support a bioprocess for the remediation of acid mine drainage containing significant concentrations of cyanide and other ions.

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The U.S. Bureau of Mines-Reno Research Center is conducting research on the chemical treatment of process waste waters by ion elutriation for removing low levels of anions from cyanide solutions. This research has been coordinated with other centers for developing a waste water treatment system.

The U.S. Bureau of Mines-Salt Lake Research Center is conducting research to develop new biohydrometallurgical techniques to decontaminate mining and milling wastes containing heavy metals and toxic chemicals. Bacterial techniques are being developed to remove cyanide and selenium from waste water.

The Bureau of Mines-Reno Research Center is conducting research to identify and quantify noxious metals and compounds, including cyanide, that must be removed from leaching wastes and to develop a technology to be applied during closure to render leaching wastes compatible with the environment. This research has involved developing closure data and rinsing techniques for leaching operations and conducting field studies to identify compounds and species in leaching wastes.

The National Institute of General Medical Sciences is funding research at Selma University, Selma, Alabama, on the biodegradation of sodium cyanide in a fixed reactor.

The German Ministry for Research and Technology is funding research at the Bergbau-Forschung GmbH, Research Institute of the Coal Mining Society, Essen, Germany, on biological treatments of effluents from coal upgrading plants. Special cultures will be developed to improve the biological purification performance, particularly with regard to the degradation of xenobiotics, cyanide and rhodanide.

The National Institute of Environmental Health Sciences is funding research at the University of Nevada at Reno on the chemical environmental problems associated with mining of gold and silver in the desert environment of the western United States. Cyanide will be the focus of an environmental chemistry project which is intended to provide essential site and chemical characterization information to concurrent biomedical projects. This research will provide information on releases of cyanide to the environment from precious metal mining and help to determine the threat to human health (i.e., potential for human exposures to cyanide) from toxic mining waste.

The U.S. Bureau of Mines-Tuscaloosa Research Center is conducting research to determine the composition of cyanide leached gold tailings and identify the constituents leached from those tailings through laboratory and field studies. Results of this research should increase understanding of the

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environmental impact of untreated fine tailings generated from gold milling operations, especially in humid climates and should also provide useful information in evaluating the regulations promulgated by the U.S. EPA and the individual state regulatory agencies on the impoundment and abandonment of the tailings.

The U.S. Bureau of Mines-Spokane Research Center is conducting research on the environmental impacts of placing mine wastes underground as backfill. This work includes a review of residual cyanide in placed landfill, water quality monitorings at two mines and laboratory tests of cyanide fate in underground environments and permeability/leachate effects through cemented tailings.

The Maine Department of Transportation is funding research at Maine University, Orono, Maine, to monitor the levels of simple cyanide and complex cyanides, pH, Na, and Cl in surface waters which are in the proximity of four Maine Department of Transportation salt storage facilities.

The U.S. Department of the Interior is conducting research under the U.S. Geological Survey to determine the impacts of highway de-icing chemicals on the groundwater quality of shallow, unconsolidated aquifers in Ohio, and to determine the salt concentration present in the soil and unsaturated zones. This research will include some analyses for dissolved cyanide in monthly samples from eight sites across Ohio.

6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting and/or measuring and monitoring cyanide in environmental media and in biological samples. The intent is not to provide an exhaustive list of analytical methods that could be used to detect and quantify cyanide. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used to detect cyanide in environmental samples are the methods approved by federal organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that refine previously used methods to obtain lower detection limits, and/or to improve accuracy and precision.

6.1 BIOLOGICAL SAMPLES

Humans may be exposed to cyanide from dietary, industrial, environmental, and other sources. Inhalation of tobacco smoke is an important source of cyanide, and exposure may occur from smoke due to fires. After absorption, cyanide is rapidly distributed in the body through blood. Some of the common methods available for determining cyanide in biological media are reported in Table 6-1. Since cyanide forms volatile hydrogen cyanide gas, tissue sampling techniques, storage, and cyanide analysis must be done with caution. The choice of tissues and the factors influencing measured cyanide concentrations are also important (Ballantyne 1983c).

The determination of cyanide in body fluids requires the separation of cyanide from thiocyanate, usually by distillation of cyanides or microdiffusion into an absorber solution. The cyanide is measured spectrophotometrically after a calorimetric reaction. Detection limits are in the low ppb range (ng/mL) (Ganjeloo et al. 1980; Laforge et al. 1994). Most of these techniques are time-consuming, and some lack specificity or sensitivity. Cyanide in blood is almost exclusively localized to the erythrocytes, whereas thiocyanate is confined to plasma (Lundquist and Sorbo 1989); thus, some researchers recommend analysis of erythrocytes (McMillan and Svoboda 1982; Sano et al. 1992). Some interferences can be mitigated. For example, sodium thiosulfate, a common cyanide antagonist that acts as an interference, can be eliminated by using a buffered solution at pH 5.2 as the acidifying agent for cyanide microdiffusion (Sylvester et al. 1982; Way 1984).

Table 6-1. Analytical Methods for Determining Cyanide in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Blood	Separation in a microdiffusion cell; treatment of absorber solution with chloramine T-phosphate and pyridine-pyrazolone reagent	Spectrophotometry (total cyanide)	0.1 ppm	No data	Morgan and Way 1980
Blood	Separation in a microdiffusion cell; treatment of absorber solution with p-benzoquinone	Spectrofluorometry (total cyanide)	0.025 ppm	No data	Ganjeloo et al. 1980
Plasma	Deproteinization with trichloroacetic acid; bromination of supernatant and treatment with pyridine-p-phenylene diamine	Spectrophotometry (thiocyanate-cyanide determination)	≈0.07 ppm	96 (thiocyanate)	Pettigrew and Fell 1972
Erythrocyte suspension	Sample purged; absorption of hydrogen cyanide in sodium hydroxide; conversion of thiocyanate to cyanide by potassium permanganate oxidation	Spectrophotometry (thiocyanate-cyanide determination)	No data	93–97	McMillan and Svoboda 1982
Blood cells	Separation of cells by centrifugation; extraction; derivitization	HPLC with fluorescence detection	2 ng/mL	83	Sano et al. 1992
Blood	Acidification of sample in a sealed vial	Headspace GC/NPD	≈0.3 µg/mL	No data	Levin et al. 1990
Blood	Acidification of sample; incubation with chloramine-T in sealed vial	Headspace GC/ECD	100 µg/L	No data	Odoul et al. 1994
Blood	Separation by diffusion; color development	spectrophotometry	≈0.07 µg/mL	No data	Laforge et al. 1994
Blood	Incubation of acidified sample	GC/NPD	1 ng/mL	No data	Seto et al. 1993

Table 6-1. Analytical Methods for Determining Cyanide in Biological Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Blood	Separation in a microdiffusion cell; absorption in methemoglobin solution	Spectrophotometric (free cyanide determination)	0.4 µg/mL	≈80	Tomoda and Hashimoto 1991
Blood and liver	Treatment of HCN released from sample digestion with lead acetate and absorption with NaOH	Specific ion electrode (total cyanide)	5 µg/L	100–109 (whole blood, 0.3–130 ppb)	Egekeze and Oehme 1979
Blood and urine	Separation in a Conway microdiffusion cell; treatment of absorber solution with naphthalene-2,3-dialdehyde and taurine	Spectrophotofluorometric	0.8 ppb	66–82.6 at 0.0013–0.13 ppm (blood); 75.6–82 at 0.0013–0.13 ppm (urine)	Sano et al. 1989
Urine	Dilution of sample; bromination and treatment with pyridine- *p*-phenylenediamine	Spectrophotometric (thiocyanate-cyanide determination)	≈0.07 ppm	88 (thiocyanate at 0.6 ppm)	Pettigrew and Fell 1972
Saliva	Derivatization	HPLC/UV (thiocyanate)	2 ng (instrumental)	95–99	Liu and Yun 1993

HCN = hydrogen cyanide; HPLC = high performance liquid chromatography; NaOH = sodium hydroxide; GC = gas chromatography; ECD = electron capture detector; NPD = nitrogen-phosphorus detector; UV = ultraviolet detector.

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Low detection limits (low ng/mL) have been achieved using a headspace/gas chromatographic (GC) technique (Seto et al. 1993). The sample is acidified and incubated, and the headspace analyzed by GC with a nitrogen-specific detector (NPD) (Carseal et al. 1993; Levin et al. 1990; Seto et al. 1993). Reported recovery is good (>90%) (Carseal et al. 1993), and precision is good as well (<15% RSD) (Carseal et al. 1993; Levin et al. 1990; Seto et al. 1993). Blood samples may be treated with chloramine T prior to incubation to produce a derivative which can be determined by GC with electron capture detection (ECD). Cyanate and thiocyanate do not interfere in this method (Odoul et al. 1994). The detection limit is 5 μg/L (ppb); precision is good (<15% RSD) (Odoul et al. 1994).

Trace amounts of cyanide in blood cells may be determined using a liquid chromatographic technique with fluorescence detection (San0 et al. 1992). The blood cells are extracted and derivatized prior to chromatography. The detection limit is 2 μg/mL. Recovery is acceptable (>80%), and precision is good (<l5%RSD) (San0 et al. 1992).

Cyanide in biological tissue and fluids can be measured spectrophotometrically after reaction with methemoglobin (Tomoda and Hashimoto 1991). The detection limit is 0.4 μg/mL. Other performance data were not reported (Tomoda and Hashimoto 1991). Cyanide in urine has been determined using microdiffusion separation and calorimetric determination (Brimer and Rosling 1991). Detection limits are in the ng/L range; other performance data were not reported (Brimer and Rosling 1991).

Cyanide in the body is biotransformed to thiocyanate quickly. People may also be exposed to thiocyanate from dietary, industrial, and medical sources. The plasma concentration of thiocyanate has also been used as an index of long-term exposure to cigarette smoke (Liu and Yun 1993). Some authors have determined thiocyanate in body fluids as a measure of cyanide exposure, while others measure cyanide concentrations in body fluids as a measure of cyanide exposure.

Serum levels of thiocyanate are usually determined spectrophotometrically after a calorimetric reaction (Li et al. 1993; Olea et al. 1992). Ion exchange resin chromatography has been used to isolate thiocyanate from serum (Olea et al. 1992). Detection limits are in the ppb range (Li et al. 1993; Olea et al. 1992). Recovery and precision, where reported, are good (recovery >90%; precision <15% RSD) (Li et al. 1993). Methods are available for measuring thiocyanate in saliva by high performance liquid chromatography (HPLC) (Liu and Yun 1993) and in saliva and blood spectrophotometrically (Tominaga et al. 1991; Yamanaka et al. 1991).

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6.2 ENVIRONMENTAL SAMPLES

Hydrogen cyanide and cyanide salts are important environmental contaminants, and there are numerous
reports dealing with the identification and quantitation of cyanide in air, water, and other environmental
media. Representative examples of monitoring methods for cyanide are included in Table 6-2.

Hydrogen cyanide in environmental or workplace air is usually collected in sodium hydroxide solution,
then measured spectrophotometrically after color development (Agrawal et al. 1991; NIOSH 1989b). One
of the most significant problems in cyanide monitoring is the instability of the collected samples
(Cassinelli 1986). The collection solution is pH ≥ 11 to avoid volatilization loss of molecular hydrogen
cyanide. However, carbon dioxide from air may react with the solution during storage, thereby lowering
the pH and releasing hydrogen cyanide gas. Oxidizing agents in solution may transform cyanide during
storage and handling. Ferrocyanide and ferricyanide complexes of cyanide undergo photodecomposition
with ultraviolet light. Particulate cyanides are known to decompose in moist air with the liberation of
hydrogen cyanide. The recommended method for the storage of cyanide samples is to collect the samples
at pH 12-12.5 in closed, dark bottles and store them in a cool, dark place. It is also recommended that the
samples be analyzed immediately upon collection. The sample handling and preservation methods have
been discussed (Cassinelli 1986; Egekeze and Oehme 1979). Cyanide determination in air usually
distinguishes between two forms of cyanides: hydrogen cyanide gas and particulate cyanides. Filters are
usually used to collect particulate cyanides, and the hydrogen cyanide gas that passes through the
membrane is trapped in sodium hydroxide. The collected particulate cyanides can be quantified separately
after acid distillation. Detection limits are in the ppm range for occupational air (Dolzine et al. 1982;
NIOSH 1989a, 1989b) and sub-ppm range for ambient air (Cassinelli 1986). Reported recovery is good
(>90%) (Cassinelli 1986; Dolzine et .al. 1982; NIOSH 1989a, 1989b).

Inorganic cyanides in water can be present both as complexed and free cyanide. Cyanide in water is
usually determined in three different forms: free cyanide, cyanide amenable to chlorination, and total
cyanide. Free cyanides such as sodium cyanide, potassium cyanide, and hydrogen cyanide are readily
ionized to the cyanide ion under the conditions used in most common analytical techniques. Methods for
determining cyanide amenable to chlorination measure simple metal cyanides and most complex cyanides
with the exception of iron cyanides. Total cyanide is a measure of all cyanides including iron cyanide
complexes. Table 6-2 lists representative analytical methods for determining cyanides that may be present
in various forms. A number of standard methods are available (APHA 1992; EPA 1983a, 1992d; NIOSH
1989a, 1989b).

Table 6-2. Analytical Methods for Determining Cyanide in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Occupational air (NIOSH Method 7904)	Filtered air collected in midget impinger containing NaOH; extraction of filter with NaOH; sulfide removed.	Specific ion electrode (HCN cyanide salts)	2.5 µg CN [a]	96.7 at 5–21 mg/m^3	NIOSH 1989a
Occupational air (NIOSH Method 6010)	Collection of breathing zone air samples on adsorbent; extraction with water; treatment with barbituric acid/ pyridine reagent	Spectrophotometry (HCN)	1 µg CN [b]	~100%	NIOSH 1989b
Occupational air	Passage of filtered air through midget impinger containing NaOH; conversion of NaCN to sodium formate. Optional ion exchange clean-up.	Ion-chromatography/ amperometric detector (HCN)	5–10 ppm	100–109 at 5–20 ppm	Dolzine et al. 1982
Air	Filtered air collected in midget impinger	Ion-chromatography/ amperometric detection (HCN only)	0.04 ppm (for 2.6 L of air)	91 at air flow rate of 0.171 L/minute	Cassinelli 1986
Water (drinking, surface, saline, domestic, and industrial waste) (EPA Method 335.1)	Chlorination of sample at pH 11–12 and ClCN driven off; reflux-distillation of residual sample; absorption of released HCN in NaOH; treatment with chloramine-T and pyridine-pyrazolone or pyridine-barbituric acid	Spectrophotometry (cyanide amenable to chlorination)	No data	No data	EPA 1983a
Water (drinking, surface, saline, domestic, and industrial waste) (EPA Method 335.2)	Reflux-distillation of sample; absorption of released HCN in NaOH scrubber; treatment of absorbing solution with chloramine-T and pyridine-pyrazolone or pyridine barbituric acid	Spectrophotometry (total cyanide)	0.02 ppm	85–102 at 0.28–0.62 ppm	EPA 1983a

Table 6-2. Analytical Methods for Determining Cyanide in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Water (drinking, surface, saline, domestic, and industrial waste) (EPA Method 335.2) (EPA Method 335.3)	Reflux-distillation of sample; absorption of released HCN in NaOH; titration of absorbing solution with AgNO$_3$ in presence of p-dimethylaminobenzal-rhodanine indicator	Titrimetric (total cyanide)	1 ppm	No data	EPA 1983a
Water (drinking, surface, saline, domestic, and industrial waste) (EPA Method 335.4)	Reflux-distillation of sample; absorption of released HCN in NaOH; treatment with chloramine-T, pyridine barbituric acid	Semi-automated spectrophotometry (total cyanide)	~.02 ppm	95 (average)	EPA 1993h
Water	None	Ion-chromatography/amperometric detection (free and a few complexed cyanides)	2 ppb	100–112	Rocklin and Johnson 1983
Water	Separation of acidified sample in a microdiffusion cell; absorption in NaOH	Potentiometric (free cyanide)	0.018 mg/L CN	96.5–103.9 at 0.037–3.49 mg/L	Rubio et al. 1987
Water	None	FIA; spectrophotometric detection (free cyanide)	20 ng/mL	88–107	Ma and Liu 1992
Water	None	FIA; amperometric detection (free cyanide)	2.6 ng/mL	99–103	Nikolić et al. 1992
Water	Sample shaken in presence of quinoline and benzoyl chloride at pH 7	HPLC with spectrophotometric detection (free CN)	≈26 pg/mL	No data	Madungwe et al. 1991

Table 6-2. Analytical Methods for Determining Cyanide in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Water	None	Ion chromatography with postcolumn derivatization and fluorimetric detection (free cyanide)	0.1 ng/mL	94–96	Gamoh and Imamichi 1991
Water	Treatment of sample with NaOH and hypophosphite; passage through silver filter (free cyanide); treatment in photo cell prior to filter for total cyanide and selective oxidation for cyanides not amenable to chlorination (CNATC)	Flame AAS or graphite furnace AAS	2 ng/mL (flame AAS); 0.06 ng/mL (graphite furnace AAS	107 (free cyanide), 90.4 (CNATC), 98.1 (total cyanide)	Rosentreter and Skogerboe 1992
Water	Samples sealed in vials with nitrogen	Headspace GC/ECD (cyanogen chloride)	0.04 ng/mL	91 avg.	Xie and Reckhow 1993
Water (APHA Method 4500-CN⁻ J)	Adjustment of sample pH to 8.0–8.5 using phosphate buffer; addition of pyridine-barbituric acid	Spectrophotometry (cyanogen chloride)	0.02 µg/mL (as CN⁻) (lowest calibration)	No data	APHA 1992
Water and waste water (APHA Method 4500-CN⁻ M)	Filtration of sample; optional treatment with resin; treatment with ferric nitrate solution	Colorimetric detection (thiocyanate)	No data	71–99, 0.07–1.42 mg/L	APHA 1992
Waste or leachate (EPA Method 9010A)	Reflux-distillation of acidified sample; absorption of released HCN in NaOH; treatment with AgNO₃ and an indicator (titrimetric) or chloramine-T/pyridine-barbituric acid (colorimetric)	Titrimetric or colorimetric detection (total and amenable cyanide)	0.1–0.2 mg/L titrimetric) 0.02 mg/L (colorimetric)	(Titrimetric) 94–99 (total cyanide), 87–97 (amenable cyanide)	EPA 1992d
Waste water	Addition of sample to buffered methemoglobin	Spectrophotometry (free cyanide)	0.2 µg/mL	No data	Tomoda and Hashimoto 1991

Table 6-2. Analytical Methods for Determining Cyanide in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Waste water	None	FIA with spectrophotometric detection	3 ng/mL	98	Kubáň 1992
Waste water	Complexation of sample with 2-benzoyl-pyridine thiosemicarbazone; solvent extraction	Flame AAS (free cyanide)	4.8 ng/mL	97–101	Chattaraj and Das 1991
Solid waste or oil waste (EPA Method 9013)	Extraction of solid component with water at pH ≥ 10 and hexane	Titrimetric or colorimetric detection (soluble cyanides)	No data	60–90 (solid) 88–92 (oil)	EPA 1992e
Soil	Extraction of soil with calcium chloride solution	Ion chromatography with conductivity detection (thiocyanate)	0.02 µg/mL	≥83; average 94, depending on soil type	Brown and Morra 1991
Food (cereal and other foodstuffs)	Extraction of sample with water/acetonitrile, dried	GC/ECD at low detection voltage (free cyanide)	≈0.1 ppm	90	Heuser and Scudmore 1969
Food (soybean and soybean products)	Sample mixed with water, lead nitrate, tartaric acid, and anti-forming agent; acidification and distillation; treatment of distillate with pyridine-barbituric acid	Spectrophotometry (total cyanide)	No data	32–80	Honig et al. 1983

[a] Method detection limits depend upon the volume of air sampled; the working range is 5 to 20 mg/m^3 for a 10-L air sample.
[b] Method detection limits depend upon the volume of air sampled; the working range is 1 to 333 mg/m^3 for a 3-L sample.

AgNO$_3$ = silver nitrate; ClCN = cyanogen chloride; CN$^-$ = cyanide ion; CNATC = cyanides not amenable to chlorination (Rosentreter and Skogerboe 1992); AAS = atomic absorption spectroscopy; EPA = Environmental Protection Agency; FIA = flow injection analysis; GC/ECD = gas chromatograph/electron capture detector; HCN = hydrogen cyanide; NaOH = sodium hydroxide; NIOSH = National Institute for Occupational Safety and Health

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Procedures for extracting cyanide from aqueous matrices usually involve acidifying the sample followed by heating and refluxing to evolve hydrogen cyanide, which is then trapped in an impinger containing absorption media. Cyanide is usually measured by calorimetric, titrimetric, or electrochemical methods (for example, APHA 1992). All are subject to interference problems. Sulfide, certain oxidizing agents, nitrate or nitrite, thiocyanate, aldehydes, and ketones may interfere under acid distillation conditions, thus producing erroneous results from both calorimetric and titrimetric methods. In addition, fatty acids in samples may distill over and form soaps under alkaline titration conditions, thus causing interference in the titrimetric method (EPA 1983a, 1992d). Calorimetric methods may be based on pyridine with chloramine-T as the oxidizing agent and barbituric acid as the coupling component (EPA 1992d) or pyrazolone as the coupling agent (EPA 1983a). Low detection limits are attained (10-20 μg/L), but sulfide and thiocyanate are common interferents (Csikal and Barnard 1983; Drikas and Routley 1988). Titrimetric methods usually employ silver nitrate (EPA 1983a, 1992d); however, the detection limits are in the low mg/L range. Methods using specific ion electrodes (electrochemical) respond to numerous interferences (sulfur, chlorine, iodine, bromine, cadmium, silver, zinc, copper, nickel, and mercury) (Cassinelli 1986).

A collaborative study conducted by Britton et al. (1984) to determine the most reliable method among the three most commonly used methods (two calorimetric methods and the specific ion electrode method) showed that both pyridine-barbituric acid and pyridine-pyrazolone have similar statistical accuracy. The pyridine-barbituric acid method was preferred by Britton et al. (1984) over the pyridine-pyrazolone method for its convenience (quicker analysis time) rather than the statistical accuracy of data. The electrode method had higher data variability.

Continuous monitoring methods based on amperometric (Nikolid et al. 1992) or spectrophotometric (Kubáň 1992; Ma and Liu 1992) techniques for the quantification of free cyanide are also available. Ion chromatography with amperometric determination provides good sensitivity (2 ppb) and selectivity for free cyanide and the weak complexes of cadmium and zinc (Rocklin and Johnson 1983). Postcolumn derivatization and fluorescence detection provides low detection limits as well (0.1 ppb) (Gamoh and Imamichi 1991).

Few methods are available for the determination of the concentrations of cyanides present in soils at low levels; ion-chromatographic techniques should provide selectivity and sensitivity.

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Few methods are available for the determination of cyanogen and cyanogen chloride in environmental matrices. Methods available include gas chromatographic-flame ionization detection of cyanogen chloride and cyanogen (Brown et al. 1986), headspace gas chromatography with electron capture detection (GUECD) (Xie and Reckhow 1993) and calorimetric detection (APHA 1992). Detection limits are in the low ppb range for the calorimetric method (APHA 1992) and in the sub-ppb range for the GC/ECD method (Xie and Reckhow 1993).

Standard methods are available for measuring thiocyanate in aqueous matrices (APHA 1992; ASTM 1994a). These are calorimetric methods and are subject to interferences. In addition, thiocyanate is biodegradable so care must be exercised in sample collection, preservation, and storage. The detection limit is 100 ppb (ASTM 1994a). An automated method with good sensitivity (0.5 ppb) is available for determining thiocyanate in water and waste water (ASTM 1994b). Various methods have been reported for determination of thiocyanate in soils; however, ion chromatographic determination provides selectivity and sensitivity (20 ppb) (Brown and Morra 1991).

6.3 ADEQUACY OF THE DATABASE

Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of cyanide is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of cyanide.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce or eliminate the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

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6.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect. Besides environmental exposure, exposure to cyanide can also occur from consumption of cyanide-containing food, metabolism of certain drugs, and smoking cigarettes. Since so many factors can influence cyanide exposure, the exact correlation between cyanide concentrations in the body and its level in the environment has not been made. Therefore, measuring cyanide and/or thiocyanate levels in blood and urine cannot be used as a biomarker for exposure to low cyanide concentrations. Analytical methods of required sensitivity and reliability to detect cyanide and thiocyanate in blood, plasma, and urine of both unexposed and exposed persons are available (see Table 6-1 and Table 6-3). Further studies determining biomarkers for exposure to low cyanide concentrations would be useful.

Although certain effects, such as cyanosis and endemic goiter, have been associated with cyanide exposure (see Section 2.6.2), a positive correlation between cyanide exposure and one of its effects has not yet been established. Additional studies establishing a correlation between cyanide exposure and one of its effects will be useful in diagnosing cyanide exposure.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. The concentration of hydrogen cyanide in most ambient air is so low that it is beyond the detection limit of the standard analytical methods. An infrared absorption method of a large vertical tropospheric column was used to measure the hydrogen cyanide concentration in the troposphere (Cicerone and Zellner 1983). Similarly, ground-based millimeter wave emission spectroscopy was used to measure stratospheric concentration of hydrogen cyanide (Jaramillo et al. 1989). Since suitable standard analytical methods are unavailable, the hydrogen cyanide level in ambient air generally remains unreported. Similarly, the level of cyanogen chloride in drinking water ranges from 0.45 to 0.80 ppb (Krasner et al. 1989), which is beyond the detection limit of the standard analytical methods without concentration and trapping procedures. Cyanogen chloride in water was determined by a purge and trap GC/MS method (Krasner et al. 1989), a method that is not available to many laboratories. There is, therefore, a need to develop standard analytical methods capable of quantitating hydrogen cyanide in air and cyanogen chloride in water at levels that are generally found in these media.

Table 6-3. Analytical Methods for Determining Environmental Degradation Products of Cyanide

Analyte	Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
SCN⁻	Water	Filtration (0.45 µm)	Reversed-phase ion-pair chromatography with amperometric detection	104 ng/mL	No data	Xu et al. 1993

SCN⁻ = thiocyanate ion

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Cyanide metabolizes in the human body to thiocyanate, and its biodegradation products include ammonia, carbon dioxide, nitrate, or nitrogen (Richards and Shieh 1989). The detection of thiocyanate in body fluids may indicate cyanide exposure. Similarly, the amounts of cyanide degradation products formed in an environmental medium could be used to measure cyanide's biodegradation rate. A summary of methods for determining environmental degradation products is shown in Table 6-4. Suitable analytical methods are available to detect all of these compounds (Pettigrew and Fell 1973; Richards and Shieh 1989).

6.3.2 Ongoing Studies

As part of a 3-year contract with EPA, the Research Triangle Institute is conducting research to improve EPA Cyanide (335.x) Methods. EPA Method 335.2 has many interferences, and the laboratory is evaluating known interferents. In addition, modifications to reduce the time per analysis, lower detection limit, and improve reliability will be evaluated.

No ongoing studies regarding the determination of low levels of hydrogen cyanide in air and cyanogen chloride in water or the identification of a biological effect that correlates with exposure to cyanide were located in the available literature.

Table 6-4. Analytical Methods for Determining Biomarkers for Cyanide

Analyte	Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Thiocyanate	Human serum, urine, saliva	Extraction of buffered (pH 7) 2-benzoyl pyridine thiosemi-carbazone and sample with isoamyl acetate	Flame atomic absorption spectrometry	4 ng/mL	96–102	Chattaraj and Das 1992
Thiocyanate	Serum	Addition of acetonitrile, centrifugation, separation	Spectrophotometry	0.3 µg/mL	94	Li et al. 1993
Thiocyanate	Human urine, saliva	Derivatization of basic pH sample with pentafluorobenzyl bromide in the presence of Kryptofix 222 B polymer and extraction into methylene chloride then back extraction into isooctane	GC with ECD	0.0115 nmol (in 0.2 mL)	83–106	Chen et al. 1994
Thiocyanate	Human urine, saliva	Dilution with water then filtration (0.45 µm)	Ion chromatography utilizing ODS column coated with cetyl-dimethylamine and with UV absorbance (210 nm) detection	20 ng/mL	95–101	Michigami et al. 1992
Thiocyanate	Urine	Ion chromatography using weakly basic resin; acidification of eluate with HCl; addition of bromine water, arseneous oxide and pyridine-p-phenylene diamine	Spectrophotometry	2.5 µmol/L (lowest reported)	No data	Tominaga and Midio 1991

Table 6-4. Analytical Methods for Determining Biomarkers for Cyanide (continued)

Analyte	Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Thiocyanate	Human urine	Dilution with water then passage through disposable Toyo pack ODS and IC-SP columns	Suppressed ion chromatography with conductivity detection	200 nM	No data	Miura and Koh 1991

ECD = electron capture detector; GC = gas chromatography; IC/SP = ion chromatography/sulfopropyl type column; ODS = octadecyl silane

7. REGULATIONS AND ADVISORIES

The international, national, and state regulations and guidelines regarding cyanide in air, water, and other media are summarized in Table 7-1.

ATSDR has derived an intermediate oral minimal risk level (MRL) of 0.05 mg/kg/day for cyanide based on a NOAEL of 4.5 mg/kg/day from a study in which 10 male and 10 female rats were given 0.2-l 2.5 mg/kg/day cyanide in the drinking water for 13 weeks, as sodium cyanide (NTP 1993).

EPA reference doses (RfDs) have been established for cyanide and its compounds. These RfDs range from $2x10^{-1}$ mg/kg/day for potassium cyanide to $5x10^{-3}$ mg/kg/day for copper cyanide. The RfD for potassium silver cyanide was based on weight loss and thyroid effects in several rat studies (Howard and Hanzel 1955; Philbrick et al. 1979), while the RfD for copper cyanide was based on decreased body and organ weights and liver and kidney effects in a intermediate-duration rat study (Gerhart 1987a). An EPA reference concentration (RfC) exists only for hydrogen cyanide; this RfC is $3x10^{-3}$ mg/m^3. The RfC was based on central nervous system and thyroid effects in a human occupational study (El Ghawabi et al. 1975).

The EPA has determined that cyanide is not classifiable as to its human carcinogenicity (Group D). No cancer classifications exist for the National Toxicology Program, IRIS, or IARC (no available data).

Several cyanide compounds are on the list of chemicals regulated under "The Emergency Planning and Community Right-to-Know Act of 1986" (EPCRA) (EPA 1988c). Section 313 of Title III of EPCRA requires owners and operators of certain facilities that manufacture, import, process, or otherwise use the chemicals on this list to report annually their release of those chemicals to any environmental media.

OSHA requires employers of workers who are occupationally exposed to cyanide to institute engineering controls and work practices to reduce and maintain employee exposure at or below permissible exposure limits (PEL). The employer must use engineering and work practice controls, if feasible, to reduce exposure to or below an 8-hour time-weighted average (TWA) of 5 mg/m^3 as cyanide. Respirators must be provided and used during the time period necessary to install or implement feasible engineering and work practice controls (OSHA 1974).

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Cyanide is regulated by the Clean Water Effluent Guidelines as stated in Title 40, Sections 400-475, of the Code of Federal Regulations. For each point source category, cyanide may be regulated as amenable or total cyanide. The point source categories for which cyanide is controlled include electroplating; metal finishing; organic chemicals; plastics and synthetic fibers; hydrogen peroxide manufacturing; iron and steel; nonferrous metals; steam electri-power; ferroalloy manufacturing; pharmaceuticals; battery manufacturing; aluminum forming; nonferrous metal forming; and coil coating.

Under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), food tolerance restrictions apply to various cyanide compounds when applied to growing crops (EPA 1971a, 1975a).

Under the Resource Conservation and Recovery Act (RCRA), cyanide is listed as a hazardous waste when it is a discarded commercial chemical product, off-specification species, container residue, or spill residue (EPA 1980c); a waste from non-specific sources (EPA 198 lc); or a waste from specific sources (EPA 1981c).

Table 7-1. Regulations and Guidelines Applicable to Cyanide

Agency	Description	Information	References
INTERNATIONAL			
Guidelines			
WHO	Drinking Water Guidelines	0.1 mg/L	WHO 1984
IARC	Group (Cancer ranking)	NA	
NATIONAL			
Regulations: a. Air:			
OSHA	List of Highly Hazardous Chemicals	Yes	29 CFR 1910.119, App. A; OSHA 1974
	Permissible Exposure Limit (TWA)	5 mg/m^3 (as CN)	29 CFR 1910.1000 OSHA 1974
EPA	Chemicals Produced by SOCMI Facilities Subject to Equipment Leak Standards	Yes	40 CFR 60.489 EPA 1983b
	Chemicals Produced by Facilities Subject to Standards for SOCMI Facilities	Yes	40 CFR 60.617 EPA 1990b
	Chemicals Subject to Standards of Performance for VOC Emissions from SOCMI Distillation Operations	Yes	40 CFR 60.667 EPA 1990c
	Proposed Rule: Deminimis Emissions for Determinations Regarding Modifications to Major Sources		59 FR 15504 EPA 1994a
	Sodium cyanide	0.1 ton/yr	
	Potassium cyanide	0.1 ton/yr	
	Other cyanide compounds	5 tons/yr	
b. Water			
EPA	Designation of Hazardous Substance Under the Federal Water Pollution Control Act	Yes	40 CFR 116.4 EPA 1978a
	Reportable Quantities of Hazardous Substances Designated Pursuant to the Clean Water Act		40 CFR 117.3 EPA 1986a
	Amnonium thiocyanate	5,000 lb.	
	Calcium cyanide	10 lb.	
	Cyanogen chloride	10 lb.	
	Hydrogen cyanide	10 lb.	
	Potassium cyanide	10 lb.	
	Sodium cyanide	10 lb.	
	NPDES Permit Application	Yes	40 CFR 122.21 EPA 1983c
	NPDES Storm Water Discharges	Yes	40 CFR 122.26 EPA 1990d
	NPDES Permit Application Testing Requirements	Yes	40 CFR 122, App. D EPA 1983c
	State Program Requirements: Non-compliance and Program Reporting	Yes	40 CFR 123.45 EPA 1985b

7. REGULATIONS AND ADVISORIES

Table 7-1. Regulations and Guidelines Applicable to Cyanide (continued)

Agency	Description	Information	References
NATIONAL (cont.)			
	Proposed Rule: Great Lakes System Water Quality Standards		58 FR 20802 EPA 1993a
	Acute water quality criteria for protecting aquatic life	22 µg/L (free cyanide)	
	Chronic water quality criteria for protection of aquatic life	5.2 µg/L (free cyanide)	

	Water quality critieria for protection of human health
	      Drinking
	      Nondrinking
		8×10^5 ng/L
		6×10^7 ng/L	

	Identification of Test Procedure for Analysis of Pollutants	Yes	40 CFR 136.3 EPA 1973
	National Primary Drinking Water Regulations Inorganic Chemical Sampling and Analytical Requirements	Yes	40 CFR 141.23 EPA 1991a
	Public Notification	Yes	40 CFR 141.32 EPA 1987c
	MCLs	0.2 mg/L (as free cyanide)	40 CFR 141.62 EPA 1991a
	Proposed Rule: Drinking Water Sampling and Analytical Requirements	Yes	58 FR 65622 EPA 1993b
	Proposed Rule: Disinfection By - Product Precursor Removal Information Collection Requirements	Yes	59 FR 6332 EPA 1994b
	Effluent Limitations		
	National Pretreatment Standards		
	Removal credits	Yes	40 CFR 403.7 EPA 1984b
	Reporting requirements for POTWs and industrial users	Yes	40 CFR 403.12 EPA 1981a
	Sampling procedures	Yes	40 CFR 403, App. E EPA 1984c
	Electroplating Point Source Category Applicability and Compliance Dates	Yes	40 CFR 413 EPA 1981b
	Definitions	Yes	40 CFR 413 EPA 1981b

		1-Day Max.	4-Day Average Max.	40 CFR 413 EPA 1981b
	Pretreatment standards for existing sources			40 CFR 413 EPA 1981b
	discharging <38,000 L/day, cyanide amenable (CN, A)	5.0 mg/L	2.7 mg/L	
	discharging ≥38,000 L/day, total cyanide (CN, T)	1.9 mg/L	1.0 mg/L	

Table 7-1. Regulations and Guidelines Applicable to Cyanide (continued)

Agency	Description	Information		References
NATIONAL (cont.)				
	Organic Chemicals, Plastics, and Synthetic Fibers Category			
	General Applicability	Yes		40 CFR 414.11 EPA 1987d
	Bulk organic chemicals, applicability	Yes		40 CFR 414.70 EPA 1987d
	Direct discharge point sources with and without end-of-pipe biological treatment (total cyanide)			40 CFR 414.91 EPA 1987d 40 CFR 414.101
	1-day maximum	1,200 µg/L		EPA 1987d
	maximum monthly average	420 µg/L		
	Cyanide-bearing waste streams	Yes		40 CFR 414, App. A EPA 1987d
	Hydrogen Peroxide Manufacturing			40 CFR 415, Subpart I EPA 1982a
	Definition	Yes		
	Effluent reduction using best practicable control technology currently available (BPT):			
	1-day maximum (CN, A)	0.00040 kg/kkg		
	30-day average (CN, A)	0.00020 kg/kkg		
	Hydrogen Cyanide Production (CN, A)			40 CFR 415, Subpart AP EPA 1982a
	Effluent reduction using BPT:			
	1-day maximum	0.10 kg/kkg		
	30-day average	0.021 kg/kkg		
	Effluent reduction using best available technology economically achievable (BAT):			
	1-day maximum	0.10 kg/kkg		
	30-day average	0.021 kg/kkg		
	Iron and Steel Manufacturing			
	General definition	Yes		40 CFR 420.02 EPA 1982b
	Cokemaking subcategory (Total cyanide)	1-day maximum	30-day average	40 CFR 420 Subpart A EPA 1982b
	Effluent reduction using BPT:			
	By-product cokemaking-iron and steel	0.0657 kg/kkg	0.0219 kg/kkg	
	By-product cokemaking-merchant	0.0701 kg/kkg	0.0234 kg/kkg	

7. REGULATIONS AND ADVISORIES

Table 7-1. Regulations and Guidelines Applicable to Cyanide (continued)

Agency	Description	Information		References
NATIONAL (cont.)				
	Effluent reduction using BAT:			
	By-product cokemaking-iron and steel	0.00638 kg/kkg	0.00351 kg/kkg	
	By-product cokemaking-merchant	0.00709 kg/kkg	0.00390 kg/kkg	
	New source performance standard (NSPS):			
	By-product cokemaking-iron and steel	0.00638 kg/kkg	0.00351 kg/kkg	
	By-product cokemaking-merchant	0.00709 kg/kkg	0.00390 kg/kkg	
	Pretreatment standards for existing sources (PSES):			
	By-product cokemaking-iron and steel	0.0172 kg/kkg	0.00859 kg/kkg	
	By-product cokemaking-merchant	0.0200 kg/kkg	0.0100 kg/kkg	
	Pretreatment standards for new sources (PSNS):			
	By-product cokemaking-iron and steel	0.0172 kg/kkg	0.00859 kg/kkg	
	By-product cokemaking-merchant	0.0200 kg/kkg	0.0100 kg/kkg	
	Sintering subcategory (total cyanide)			40 CFR 420 Subpart B EPA 1982b
	Effluent reduction using BAT	0.00300 kg/kgg	0.00150 kg/kkg	
	NSPS	0.00100 kg/kgg	0.000501 kg/kkg	
	PSES	0.00300 kg/kkg	0.00150 kg/kkg	
	PSNS	0.00100 kg/kkg	0.000501 kg/kkg	
	Ironmaking subcategory (total cyanide)			40 CFR 420 Subpart C EPA 1982b
	Effluent reduction using BPT	0.0234 kg/kkg	0.00782 kg/kkg	
	Effluent reduction using BAT	0.00175 kg/kkg	0.000876 kg/kkg	
	NSPS	0.000584 kg/kkg	0.000292 kg/kkg	
	PSES -ironblast furnace	0.00175 kg/kkg	0.000876 kg/kkg	
	PSES-existing indirect discharges	0.00175 kg/kkg	0.000876 kg/kkg	
	PSNS	0.000584 kg/kkg	0.000292 kg/kkg	

Table 7-1. Regulations and Guidelines Applicable to Cyanide (continued)

Agency	Description	Information		References
NATIONAL (cont.)				
	Salt bath descaling subcategory (total cyanide)			40 CFR 420 Subpart H EPA 1982b
	Effluent reduction using BPT and BAT; NSPS; PSES; and PSNS for salt bath descaling, reducing			
	- batch	0.00102 kg/kkg	0.000339 kg/kkg	
	- continuous	0.00569 kg/kkg	0.00190 kg/kkg	
	Nonferrous Metals Manufacturing			40 CFR 421.3 EPA 1984d
	General monitoring and reporting	Yes		
	Primary aluminum smelting subcategory	1-day <u>maximum</u> (ng/kg of cryolite re-covered)	monthly average <u>maximum</u> (ng/kg of cryolite re-covered)	40 CFR 421 Subpart B EPA 1984d
	Effluent reduction using BAT, PSNS and PSNS for cathode reprocessing (operated with dry potline scrubbing commingled and not commingled with other process or nonprocess coaters	157.600	70.060	
	BAT effluent limiations for: - cathode reprocessing (with wet potline scrubbing	0.000	0.000	
	-potline wet air pollution control (operated with cathode reprocessing and commingled and not commingled with other process on nonprocess waters)	3.771	1.676	
	Primary beryllium subcategory BPT (total cyanide)			40 CFR 421, Subpart O EPA 1985c
	- minimum	0.000 mg/kg	0.000 mg/kg	
	- maximum	651.300 mg/kg	269.500 mg/kg	
	BAT, NSPS, PSNS (total cyanide) - minimum	0.000 mg/kg	0.000 mg/kg	
	- maximum	449.200 mg/kg	179.700 mg/kg	
	Secondary precious metals subcategory BPT (total cyanide) - minimum	0.000 mg/troy oz.	0.000 mg/troy oz.	40 CFR 421, Subpart X EPA 1985c
	- maximum	20.820 mg/troy oz.	8.616 mg/troy oz.	

Table 7-1. Regulations and Guidelines Applicable to Cyanide (continued)

Agency	Description	Information		References
NATIONAL (cont.)				
	BAT, NSPS, PSES, & PSNS (total cyanide)			
	- minimum	0.000 mg/troy oz.	0.000 mg/troy oz.	
	- maximum	10.000 mg/troy oz.	4.000 mg/troy oz.	
	Secondary tin subcategory BPT (total cyanide)			40 CFR 421, Subpart AA EPA 1985c
	- minimum	0.010 mg/kg	0.004 mg/kg	
	- maximum	33.35 mg/kg	13.80 mg/kg	
	BAT, NSPS, PSES, & PSNS (total cyanide)			
	- minimum	0.007 mg/kg	0.003 mg/kg	
	- maximum	23.00 mg/kg	9.20 mg/kg	
	Primary zirconium and hafnium BPT (total cyanide)			40 CFR 421, Subpart AE EPA 1985c
	- minimum	0.000 mg/kg	0.000 mg/kg	
	- maximum	12.610 mg/kg	5.216 mg/kg	
	BAT, NSPS, PSNS (total cyanide) - minimum	0.000 mg/kg	0.000 mg/kg	
	- maximum	8.694 mg/kg	3.478 mg/kg	
	Steam Electric Power Generating: Priority Pollutants	Yes		40 CFR 423, App A EPA 1982c
	Ferroalloy Manufacturing: Covered Electric Furnaces	1-day maximum	30-day average	40 CFR 424 Subpart B EPA 1974
	BPT (total cyanide)	0.004 kg/Mwh	0.002 kg/Mwh	
	BAT & NSPS (total cyanide)	0.0005 kg/Mwh	0.0003 kg/Mwh	
	Ferroalloy Manufacturing: Covered			40 CFR 424 Subpart D EPA 1975a
	Calcium carbide furnace BPT & BAT (total cyanide)	0.0056 kg/kkg	0.0028 kg/kkg	
	Metal finishing BPT, BAT, PSES, & PSNS (total cyanide) BPT, BAT, PSES & PSNS (amenable cyanide)	1.20 mg/L 0.86 mg/L	0.65 mg/L 0.32 mg/L	40 CFR 433 Subpart A EPA 1983d

7. REGULATIONS AND ADVISORIES

Table 7-1. Regulations and Guidelines Applicable to Cyanide (continued)

Agency	Description	Information		References
NATIONAL (cont.)				
	Pharmaceutical Manufacturing			40 CFR 439 EPA 1983e
	BPT, BAT, NSPS, PSES, & PSNS (total cyanide)	33.5 mg/L	9.4 mg/L	
	Battery Manufacturing: Zinc Subcategory (total cyanide)			40 CFR 461 Subpart G EPA 1984e
	BPT	2.54 mg/kg	1.05 mg/kg	
	BAT, PSES	0.38 mg/kg	0.16 mg/kg	
	NSPS, PSNS	0.039 mg/kg	0.016 mg/kg	
	Coil Coating			40 CFR 465 EPA 1982d
	Monitoring and reporting	Yes		
	Steel basis material subcategory	1-day maximum	Monthly avg. maximum	
	BPT	0.80 mg/m^2	0.33 mg/m^2	
	BAT, PSES	0.34 mg/m^2	0.14 mg/m^2	
	NSPS, PSNS	0.063 mg/m^2	0.025 mg/m^2	
	Galvanized basis material subcategory			
	BPT	0.76 mg/m^2	0.32 mg/m^2	
	BAT, PSES	0.26 mg/m^2	0.11 mg/m^2	
	NSPS, PSNS	0.07 mg/m^2	0.028 mg/m^2	
	Aluminum basis material subcategory			
	BPT	0.98 mg/m^2	0.41 mg/m^2	
	BAT, PSES	0.29 mg/m^2	0.12 mg/m^2	
	NSPS, PSNS	0.095 mg/m^2	0.038 mg/m^2	
	Aluminum Forming Monitoring	Yes		40 CFR 467 EPA 1983f

Table 7-1. Regulations and Guidelines Applicable to Cyanide (continued)

Agency	Description	Information		References
NATIONAL (cont.)				
	Rolling with neat oil subcategory	1-day maximum	Monthly avg. maximum	
	BPT (total cyanide)			
	- minimum	0.00057 mg/off-kg	0.00024 mg/off-kg	
	- maximum	4.61 mg/off-kg	1.91 mg/off-kg	
	BAT (total cyanide)			
	- minimum	0.00057 mg/off-kg	0.00024 mg/off-kg	
	- maximum	4.04 mg/off-kg	1.67 mg/off-kg	
	NSPS (total cyanide)			
	- minimum	0.00039 mg/off-kg	0.00016 mg/off-kg	
	- maximum	0.41 mg/off-kg	0.17 mg/off-kg	
	PSES (total cyanide)			
	- minimum	0.00057 mg/off-kg	0.00024 mg/off-kg	
	- maximum	0.59 mg/off-kg	0.25 mg/off-kg	
	PSNS (total cyanide)			
	- minimum	0.00039 mg/off-kg	0.00016 mg/off-kg	
	- maximum	0.41 mg/off-kg	0.17 mg/off-kg	
	Rolling with emulsions subcategory BPT (total cyanide)			
	- minimum	0.038 mg/off-kg	0.016 mg/off-kg	
	- maximum	4.61 mg/off-kg	1.91 mg/off-kg	
	BAT, PSES (total cyanide)			
	- minimum	0.038 mg/off-kg	0.016 mg/off-kg	
	- maximum	0.59 mg/off-kg	0.25 mg/off-kg	
	NSPS, PSNS (total cyanide)			
	- minimum	0.026 mg/off-kg	0.011 mg/off-kg	
	- maximum	0.41 mg/off-kg	0.16 mg/off-kg	
	Extrusion subcategory BPT (total cyanide)			
	- minimum	0.052 mg/off-kg	0.022 mg/off-kg	
	- maximum	4.61 mg/off-kg	1.91 mg/off-kg	

7. REGULATIONS AND ADVISORIES

Table 7-1. Regulations and Guidelines Applicable to Cyanide (continued)

Agency	Description	Information		References
NATIONAL (cont.)				
	BAT, PSES (total cyanide)			
	- minimum	0.052 mg/off-kg	0.022 mg/off-kg	
	- maximum	1.2 mg/off-kg	0.5 mg/off-kg	
	NSPS (total cyanide)			
	- minimum	0.036 mg/off-kg	0.024 mg/off-kg	
	- maximum	0.41 mg/off-kg	0.17 mg/off-kg	
	PSNS (total cyanide)			
	- minimum	0.036 mg/off-kg	0.015 mg/off-kg	
	- maximum	0.41 mg/off-kg	0.17 mg/off-kg	
	Forging subcategory NSPS, PSNS (total cyanide)			
	- minimum	0.010 mg/off-kg	0.004 mg/off-kg	
	- maximum	0.41 mg/off-kg	0.163 mg/off-kg	
	PSES			
	- minimum	0.015 mg/off-kg	0.006 mg/off-kg	
	- maximum	1.2 mg/off-kg	0.5 mg/off-kg	
	Drawing with neat oil subcategory BPT (total cyanide)			
	- minimum	0.00057 mg/off-kg	0.00024 mg/off-kg	
	- maximum	4.61 mg/off-kg	1.91 mg/off-kg	
	BAT			
	- minimum	0.0006 mg/off-kg	0.0002 mg/off-kg	
	- maximum	0.591 mg/off-kg	0.245 mg/off-kg	
	NSPS, PSNS			
	- minimum	0.0004 mg/off-kg	0.0002 mg/off-kg	
	- maximum	0.408 mg/off-kg	0.163 mg/off-kg	
	PSES			
	- minimum	0.0006 mg/off-kg	0.0003 mg/off-kg	
	- maximum	0.591 mg/off-kg	0.245 mg/off-kg	

Table 7-1. Regulations and Guidelines Applicable to Cyanide (continued)

Agency	Description	Information		References
NATIONAL (cont.)	Drawing with emulsions of soaps subcategory			
	BPT			
	- minimum	0.0006 mg/off-kg	0.0003 mg/off-kg	
	- maximum	4.61 mg/off-kg	1.91 mg/off-kg	
	BAT, PSES			
	- minimum	0.0006 mg/off-kg	0.0003 mg/off-kg	
	- maximum	0.591 mg/off-kg	0.25 mg/off-kg	
	NSPS, PSNS			
	- minimum	0.0004 mg/off-kg	0.0002 mg/off-kg	
	- maximum	0.408 mg/off-kg	0.16 mg/off-kg	
	Nonferrous Metals Forming & Metal Powders			40 CFR 471 EPA 1985d
	Precious metal forming	1-day maximum	Maximum monthly average	
	BPT			
	- minimum	0.0009 mg/off-kg	0.0004mg /off-kg	
	- maximum	3.51 mg/off-kg	1.45 mg/off-kg	
	BAT, NSPS, PSES, PSNS			
	- minimum	0.0009 mg/off-kg	0.0004 mg/off-kg	
	- maximum	1.94 mg/off-kg	0.802 mg/off-kg	
	Titanium forming subcategory			
	BPT			
	- minimum	0.010 mg/off-kg	0.004 mg/off-kg	
	- maximum	8.47 mg/off-kg	3.51 mg/off-kg	
	BAT, NSPS, PSES, PSNS			
	- minimum	0.010 mg/off-kg	0.005 mg/off-kg	
	- maximum	0.84 mg/off-kg	0.351 mg/off-kg	
	Zinc forming subcategory			
	BPT			
	- minimum	0.0004 mg/off-kg	0.0002 mg/off-kg	
	- maximum	1.04 mg/off-kg	0.430 mg/off-kg	

Table 7-1. Regulations and Guidelines Applicable to Cyanide (continued)

Agency	Description	Information		References
NATIONAL (cont.)				
	BAT, NSPS, PSNS			
	- minimum	0.0003 mg/off-kg	0.0001 mg/off-kg	
	- maximum	0.338 mg/off-kg	0.135 mg/off-kg	
	Zirconium-hafrium forming subcategory			
	BPT			
	- minimum	0.005 mg/off-kg	0.002 mg/off-kg	
	- maximum	9.11 mg/off-kg	3.77 mg/off-kg	
	BAT, NSPS, PSES, PSNS			
	- minimum	0.005 mg/off-kg	0.002 mg/off-kg	
	- maximum	0.911 mg/off-kg	0.377 mg/off-kg	
	Metal powders subcategory			
	BPT			
	- minimum	0.004 mg/off-kg	0.002 mg/off-kg	
	- maximum	2.55 mg/off-kg	1.06 mg/off-kg	
	BAT, PSES			
	- minimum	0.004 mg/off-kg	0.002 mg/off-kg	
	- maximum	2.55 mg/off-kg	1.06 mg/off-kg	
	NSPS, PSNS			
	- minimum	0.004 mg/off-kg	0.002 mg/off-kg	
	- maximum	2.29 mg/off-kg	0.948 mg/off-kg	
c. Food				
EPA	Tolerances for Related Pesticide Chemicals	Yes		40 CFR 180.3 EPA 1976
	Tolerances for Residues of Calcium Cyanide:			40 CFR 180.125 EPA 1971
	Grains	25 ppm		
	Cucumbers, lettuce, radishes and tomatoes	5 ppm		
	Tolerances for Residues of Hydrogen Cyanide:	25 - 250 ppm		40 CFR 180.130 EPA 1971
	Exemptions From the Requirement of a Tolerance	Yes		40 CFR 180.1001 EPA 1971
	Tolerances for Pesticides in Food (Hydrogen Cyanide):	50 - 200 ppm		40 CFR 185.3600 EPA 1975b

7. REGULATIONS AND ADVISORIES

Table 7-1. Regulations and Guidelines Applicable to Cyanide (continued)

Agency	Description	Information	References
NATIONAL (cont.)			
d. Other EPA	Pesticides Classified for Restricted Use	Yes	40 CFR 152.175 EPA 1978b
	List of Hazardous Constituents	Yes	40 CFR 258, App. II EPA 1991b
	Definition of Hazardous Waste	Yes	40 CFR 261.3 EPA 1992a
	Characteristics of Reactivity	Yes	40 CFR 261.23 EPA 1980b
	Hazardous Waste from Nonspecific Sources	Yes	40 CFR 261.31 EPA 1981c
	Discarded Commercial Chemical Products, Off-specification Species, Container Residues, and Spill Residues	Yes	40 CFR 261.33 EPA 1980c
	Basis for Listing Hazardous Waste	Yes	40 CFR 261, App. VII EPA 1981c
	Hazardous Constituents	Yes	40 CFR 261, App. VIII EPA 1988b
	Excluded Waste	Yes	40 CFR 261, App. IX EPA 1984f
	Disposal in Landfills of Small Containers of Hazardous Waste in Overpacked Drums	Yes	40 CFR 264.316 EPA 1982e
	Recordkeeping Instructions for Hazardous Waste TSDF	Yes	40 CFR 264, App I EPA 1980c
	Hazardous Waste TSDF - Incompatible Waste	Yes	40 CFR 264, App V EPA 1981d
	Groundwater Monitoring List for Hazardous Waste TSDF	Yes	40 CFR 264, App IX EPA 1987e
	Interim Status Standards for Hazardous Waste TSDF - Recordkeeping	Yes	40 CFR 265, App, I EPA 1980d
	Interim Status Standards for Hazardous Waste TSDF - Potentially Incompatible Waste	Yes	40 CFR 265, App V EPA 1980d
	Health-Based Limits for Exclusion of Waste - Derived Residues:		40 CFR 266, App VII EPA 1991c
	Calcium cyanide	1×10^{-6} mg/kg	
	Copper cyanide	2×10^{-1} mg/kg	
	Cyanogen; sodium cyanide	1 mg/kg	
	Hydrogen cyanide	7×10^{-5} mg/kg	
	Potassium cyanide	2 mg/kg	
	Potassium silver cyanide	7 mg/kg	
	Land Disposal - Dilution Prohibited as a Substitute for Treatment	Yes	40 CFR 268.3 EPA 1990e
	Land Disposal - Wastes to be Evaluated by August 8, 1988	Yes	40 CFR 268.10 EPA 1986b

Table 7-1. Regulations and Guidelines Applicable to Cyanide (continued)

Agency	Description	Information		References
NATIONAL (cont.)	Land Disposal - Wastes to be Evaluated by June 8, 1989	Yes		40 CFR 268.11 EPA 1986b
	Land Disposal - Wastes to be Evaluated by May 8, 1990	Yes		40 CFR 268.12 EPA 1986b
	Land Disposal - Ignitable and Corrosive Wastes Whose Treatment Standards Were Vacated	Yes		40 CFR 268.37 EPA 1993c
	Land Disposal - Treatment Standards Expressed as Concentrations in Waste Extract	Wastewater	Non-wastewater	40 CFR 268.41 EPA 1986b
	Waste code PO99, potassium silver cyanide	NA	0.072 mg/L	
	Land Disposal - Treatment Standards Expressed as Specified Technologies	Yes		40 CFR 268.42 EPA 1986b
	Land Disposal - Treatment Standards Expressed as Waste Concentrations	Wastewater	Non-wastewater	40 CFR 268.43 EPA 1988c
	D003 (total cyanides)	(reserved)	590 mg/kg	
	D003 (amenable cyanides)	0.86 mg/L	30 mg/kg	
	F006, F019 (total cyanides)	1.2 mg/L	590 mg/kg	
	F006, F019 (amenable cyanides)	0.86 mg/L	30 mg/kg	
	F007, F008, F009 (total cyanides)	1.9 mg/L	590 mg/kg	
	F007, F008, F009 (amenable cyanides)	0.1 mg/L	30 mg/kg	
	F010 (total cyanides)	1.9 mg/L	1.5 mg/kg	
	F010 (amenable cyanides)	0.1 mg/L	NA	
	F011, F012, P013, P021, P029, P030, P063, P074, P098, P099, P104, P106, P121 (total cyanides)	1.9 mg/L	110 mg/kg	
	F011, F012, P013, P021, P029, P030, P063, P074, P098, P099, P104, P106, P121 (amenable cyanides)	0.1 mg/L	9.1 mg/kg	
	F037, K048, K049, K050, K051, K052 (total cyanides)	0.028 mg/L	1.8 mg/kg	
	K005, K007 (total cyanides)	0.74 mg/L	reserved	
	K011, K013, K014 (total cyanides)	21 mg/L	57 mg/kg	
	K060	1.9 mg/L	1.2 mg/kg	
	K086	1.9 mg/L	1.5 mg/kg	
	Land Disposal - Variance From Treatment Standards	Yes		40 CFR 268.44 EPA 1986b
	Land Disposal - Treatment of Hazardous Debris	Yes		40 CFR 268.45 EPA 1992b

Table 7-1. Regulations and Guidelines Applicable to Cyanide (continued)

Agency	Description	Information	References
NATIONAL (cont.)	Land Disposal - Alternative Treatment Standards	Yes	40 CFR 268.46 EPA 1992b
	Proposed Rule - Treatment Standards for Land Disposal	Yes	58 FR 48092 EPA 1993d
	NCP Chemicals-Use of Dispersants and Other	Yes	40 CFR 300.915 EPA 1990f
	NCP-Dispersant Effectiveness and Toxicity	Yes	40 CFR 300, App C EPA 1984g
	Proposed Rule - NCP Data Requirements	Yes	58 FR 54702 EPA 1993e
	List of Hazardous Substances and Reportable Quantities		40 CFR 302.4 EPA 1985e
	Ammonium thiocyanate	5,000 lbs	
	Calcium cyanide, cyanogen chloride, sodium cyanide, copper cyanide	10 lbs	
	Cyanides (soluble salts & complexes)	10 lbs	
	Cyanogen	100 lbs	
	Potassium silver cyanide	1 lb	
	Proposed Rule - Reportable Quantity Adjustments	Yes	58 FR 54836 EPA 1993f
	Emergency Planning - Extremely Hazardous Substances and Their Threshold Planning Quantities		40 CFR 355, App A EPA 1987f
	Potassium cyanide, sodium cyanide	100 lbs	
	Potassium silver cyanide	500 lbs	
	Toxic Chemical Release Reporting - List of Chemicals	Yes	40 CFR 372.65 EPA 1988d
	Chemical Information Rules - Chemical List	Yes	40 CFR 712.30 EPA 1982f
Guidelines: a. Air:			
ACGIH	Threshold Limit Values for Occupational Exposure (TLV-TWA)		ACGIH 1996
	Cyanogen	21 mg/m^3	
	TLV - Ceiling		
	Hydrogen cyanide, sodium cyanide, calcium cyanide, potassium cyanide, acetone cyanohydrin	5 mg/m^3	
	Cyanogen chloride	0.75 mg/m^3	
NIOSH	Recommended Exposure Limit for Occupational Exposure (TWA)		NIOSH 1992
	Cyanogen	20 mg/m^3	
	Recommended Exposure Limit for Occupational Exposure (Ceiling)		
	Calcium, hydrogen, potassium, and sodium cyanide	5 mg/m^3	
	Cyanogen chloride	0.6 mg/m^3	

7. REGULATIONS AND ADVISORIES

Table 7-1. Regulations and Guidelines Applicable to Cyanide (continued)

Agency	Description	Information	References
NATIONAL (cont.)	Immediately Dangerous to Life & Health Potassium and sodium cyanide Hydrogen cyanide	 50 mg/m^3 50 ppm	NIOSH 1990
b. Water: EPA	1-d Health Advisory (cyanide)	0.22 mg/L (child)	EPA 1995
	10-d Health Advisory (cyanide)	0.22 mg/L (child)	
	Lifetime Health Advisory (cyanide)	0.2 mg/L (adult)	
	Longer-term Health Advisory (cyanide)	0.2 mg/L (child) 0.8 mg/L (adult)	
	Maximum Contaminant Level	0.2 mg/L	EPA 1995
	Copper cyanide, cyanide, potassium silver cyanide, sodium cyanide		
	Maximum Contaminant Level Goal		
	Cyanide, potassium silver cyanide, sodium cyanide, potassium cyanide	0.2 mg/L	IRIS 1996
	Copper cyanide	1.3 mg/L	
	Potassium cyanide	0.2 mg/L (cyanide)	
	Cancer Classification Cyanide	D[a]	
	Hazard Ranking RfD Free cyanide, hydrogen cyanide)	2x10^{-2} mg/kg/day (UF:100)	
	Calcium cyanide, cyanogen, sodium cyanide	4x10^{-2} mg/kg/day (UF:100)	
	Copper cyanide	5x10^{-3} mg/kg/day (UF:1000)	
	Potassium cyanide, cyanogen chloride	5x10^{-2} mg/kg/day (UF:100)	
	Potassium silver cyanide	2x10^{-1} mg/kg/day (UF:100)	
	RfC Hydrogen cyanide	3x10^{-3} mg/m^3 (UF:1000)	
	Ambient Water Quality Criteria for Human Health Potassium silver cyanide, sodium cyanide, potassium cyanide, copper cyanide	2x10^2 µg/L (water and fish)	
	Ambient Water Quality Criteria for Aquatic Organisms Sodium cyanide, potassium cyanide	2.2x10^1 µg/L (freshwater acute) 5.2 µg/L (freshwter chronic) 1 µg/L (marine acute)	

Table 7-1. Regulations and Guidelines Applicable to Cyanide (continued)

Agency	Description	Information	References
NATIONAL (cont.)			
	Copper cyanide	9.2 µg/L (freshwater acute) 6.5 µg/L (freshwater chronic) 2.9 µg/L (marine acute)	
STATE			
Regulations and Guidelines: a. Air			
	Average acceptable ambient air concentrations		NATICH 1992
AZ Hydrogen cyanide	1-hour average 24-hour average	40 µg/m^3 40 µg/m^3	
CT Cyanides Hydrogen cyanide Cyanogen	8-hour average 8-hour average 8-hour average	100 µg/m^3 220 µgm/^{3} 400 µg/m^3	
FL-Ft Ldle Cyanide Hydrogen cyanide Cyanogen	8-hour average 8-hour average 8-hour average	0.5 mg/m^3 0.1 mg/m^3 0.2 mg/m^3	
FL-Pinella Hydrogen cyanide	8-hour average 24-hour average Annual	100 µg/m^3 24 µg/m^3 20 µg/m^3	
Potassium cyanide	8-hour average 24-hour average Annual	50 µg/m^3 12.0 µg/m^3 50.0 µg/m^3	
Calcium cyanide	Annual	30.0 µg/m^3	
Copper(1) cyanide	Annual	5.00 µg/m^3	
Cyanogen	8-hour average 24-hour average Annual	200 µg/m^3 48.0 µg/m^3 30.0 µg/m^3	
Cyanogen chloride	8-hour average 24-hour average	6.00 µg/m^3 1.44 µg/m^3	
FL-Tampa Cyanide Cyanogen	8-hour average 8-hour average	0.05 mg/m^3 0.2 mg/m^3	
LA Hydrogen cyanide	8-hour average	260 µg/m^3	

Table 7-1. Regulations and Guidelines Applicable to Cyanide (continued)

Agency	Description	Information	References
STATE (cont.)			
NV			
Hydrogen cyanide	8-hour average	0.238 mg/m^3	
Potassium cyanide	8-hour average	0.119 mg/m^3	
Cyanogen	8-hour average	0.476 mg/m^3	
Cyanogen chloride	8-hour average	0.014 mg/m^3	
NY			
Cyanide	1-year average	16.7 µg/m^3	
Hydrogen cyanide	1-year average	33.0 µg/m^3	
Potassium cyanide	1-year average	17.0 µg/m^3	
Cyanogen	1-year average	66.7 µg/m^3	
NC			
Hydrogen cyanide	1-hour average	1.10 mg/m^3	
	24-hour average	0.14 mg/m^3	
NC-For. Co.			
Hydrogen cyanide	1-hour average	1.10 mg/m^3	
	24-hour average	0.14 mg/m^3	
ND			
Cyanide	8-hour average	0.05 mg/m^3	
Hydrogen cyanide	1-hour average	0.11 mg/m^3	
Cyanogen	8-hour average	0.21 mg/m^3	
Cyanogen chloride	1-hour average	0.0075 mg/m^3	
OK			
Hydrogen cyanide	24-hour average	51.0 µg/m^3	
SC			
Cyanide	24-hour average	125 µg/m^3	
Hydrogen cyanide	24-hour average	250 µg/m^3	
Cyanogen	24-hour average	500 µg/m^3	
SD			
Cyanide	8-hour average	100 µg/m^3	

Table 7-1. Regulations and Guidelines Applicable to Cyanide (continued)

Agency	Description	Information	References
STATE (cont.)			
TX			
Cyanide	30-minute average	50 $\mu g/m^3$	
Hydrogen cyanide	Annual	5 $\mu g/m^3$	
Potassium cyanide	30-minute average Annual	50 $\mu g/m^3$ 5 $\mu g/m^3$	
Cyanogen	30-minute average Annual	210 $\mu g/m^3$ 21.0 $\mu g/m^3$	
Cyanogen chloride	30-minute average Annual	7.50 $\mu g/m^3$ 0.75 $\mu g/m^3$	
VA			
Cyanide	24-hour average	83 $\mu g/m^3$	
Hydrogen cyanide	24-hour average	92 $\mu g/m^3$	
Cyanogen	24-hour average	350 $\mu g/m^3$	
Cyanogen chloride	24-hour average	6.3 $\mu g/m^3$	
VT			
Cyanide	8-hour average	500 $\mu g/m^3$	
WA-SWest			
Hydrogen cyanide	24-hour average	33.3 $\mu g/m^3$	
Potassium cyanide	24-hour average	16.7 $\mu g/m^3$	
Cyanogen	24-hour average	66.6 $\mu g/m^3$	
Cyanogen chloride	24-hour average	2.00 $\mu g/m^3$	
b. Water:			
	Water Quality: Human Health		
AZ	Drinking water guideline	220 $\mu g/L$	FSTRAC 1990
FL	Domestic/Drinking	200 $\mu g/L$	Sittig 1994
KS	Drinking water guideline	154 $\mu g/L$	FSTRAC 1990
MA	Drinking water guideline	140 $\mu g/L$	
ME	Drinking water guideline	154 $\mu g/L$	
MI	Domestic/Drinking	150 $\mu g/L$ (free)	Sittig 1994
MN	Drinking water guideline	154 $\mu g/L$	FSTRAC 1990
NH	Drinking water guideline	154 $\mu g/L$	
NJ	Domestic/Drinking	200 $\mu g/L$	Sittig 1994
NY	Domestic/Drinking	100 $\mu g/L$	
OR	Domestic/Drinking	200 $\mu g/L$	
RI	Drinking water guideline	150 $\mu g/L$	FSTRAC 1990
TN	Domestic/Drinking	200 $\mu g/L$	Sittig 1994
VT	Drinking water standard	154 $\mu g/L$	FSTRAC 1990

Table 7-1. Regulations and Guidelines Applicable to Cyanide (continued)

Agency	Description	Information	References
STATE (cont.)	Water Quality: Human Health		CELDs 1994
AL	Consumption of water and fish	No value given	
	Fish consumption only	No value given	
AZ	Domestic water source (DWS)	140 µg/L (T)	
	Fish consumption (FC)	210,000 µg/L (T)	
	Full body contact (FBC)	3,100 µg/L (T)	
	Partial body contact (PBC)	3,100 µg/L (T)	
CT	Degree of treatment		
	Disinfection and chemical	0.01 mg/L	
	Complete	0.2 mg/L	
	Maximum permissible level	0.2 mg/L	
CO		0.20 mg/L	
DC	Class C	0.003 mg/L	
	Class D	0.2 mg/L	
FL	MCL	0.2 mg/L	
	Criteria for surface waters, Class I - V	5.0 µg/L	
HI	Freshwater: acute	22 µg/L	
	Freshwater: chronic	5.2 µg/L	
	Saltwater: acute	1 µg/L	
	Saltwater: chronic	1 µg/L	
	Fish consumption	No standard (NS)	
IA	MCL: Class B waters	0.005 mg/L	
	Class C waters	0.02 mg/L	
IL	MCL	0.2 mg/L	
ID	MCL	0.2 mg/L	
IN	Continuous (4-day average) Point of Water Intake	200 µg/L	
KY	Maximum Allowable Instream Concentration (free cyanide)		
	Chronic	5 µg/L	
	Acute	22 µgL	
	MCL: Domestic Water Supply (free cyanide)	0.200 mg/L	
MN	Class A & B Waters (CN)	0.01 mg/L	
	Class D Waters (CN)	0.2 mg/L	
MS	Freshwater: Acute	22 µg/L	
	Chronic	5.2 µg/L	
	Saltwater: Acute	1.0 µg/L	
	Chronic	1.0 µg/L	
NH	MCL (CN)	0.01 mg/L	
	Municipal/Domestic	0.2 mg/L	
NJ	Ground-water Quality: Class GWI	0.2 mg/L	
	GW2 & GW3	0.2 mg/L	
NM	Groundwater (CN)	0.2 mg/L	

Table 7-1. Regulations and Guidelines Applicable to Cyanide (continued)

Agency	Description	Information	References
STATE (cont.)			
NY	Groundwater Effluent Standards: Max. Allowable Concentration	400 µg/L	
	Surface Waters and Groundwater		
	A, A-S, AA, AA-S	100 µg/L	
	GA	100 µg/L	
	Freshwater	5.2-22 µg/L	Sittig 1994
	Saltwater	1.0 µg/L	
NC	Class GS Groundwater	0.154 mg/L	CELDs 1994
OH	30-day average	200 µg/L	
OK	Max. Allowable Levels	0.2 mg/L	
UT	MCL (free cyanide)	0.2 mg/L	
VA	Groundwater	0.005 mg/L	
VT	Class A or B Waters	200 µg/L	
WY	MCL - Groundwaters	0.2 mg/L	
WI	Public Water Supplier (total cyanide)		
	Warmwater sport fish communities	0.6 mg/L	
	Cold water communities	0.6 mg/L	
	Great Lakes Communities	0.6 mg/L	
	Non-Public Water Supplier (total cyanide)		
	Warmwater sport fish communities	40 mg/L	
	Cold water communities	40 mg/L	
	Warm water forage and limited forage	120 mg/L	
	fish communities and limited aquatic life		
	Groundwater	200 µg/L	
	Enforcement standard	40 µg/L	
	Preventive action limit		
WV	Water Quality Criteria (Free cyanide):		
	Warm water fishery streams	5 µg/L	
	Trout waters	5 µg/L	
	Small non-fishable streams	5 µg/L	
	Water contact, recreation	5µg/L	
	Water supply, public	5µg/L	
	Water Quality: Aquatic Life		CELDS 1994
AL	Freshwater: Acute	22.0 µg/L	
	Chronic	5.2 µg/L	
	Marine: Acute	1.0 µg/L	
	Chronic	--	

Table 7-1. Regulations and Guidelines Applicable to Cyanide (continued)

Agency	Description	Information	References
STATE (cont.)			
AZ	Acute Criteria For Aquatic & Wildlife		
	Cold water fishery (A&Wc)	22 µg/L, T(total recoverable)	
	Warm water fishery (A&Ws)	41 µg/L, T	
	Effluent dominated water (A&Wedw)	41 µg/L, T	
	Ephemeral (A&We)	84 µg/L, T	
	Chronic Criteria for Aquatic & Wildlife		
	A&Wc	5.2 µg/L, T	
	A&Ws	9.7 µg/L, T	
	A&Wedw	9.7 µg/L, T	
	A&We	19 µg/L, T	
IN	Acute Aquatic Criterion	22 µg/L	
	Continuous (4-day average) outside of mixing zone: Chronic aquatic criterion	5.2 µg/L	
MD	Ambient Surface Waters		
	Fresh water: Acute	22 µg/L	
	Chronic	5.2 µg/L	
	Estuarine: Acute	--	
	Chronic	--	
	Saltwater: Acute	1 µg/L	
	Chronic	--	
MN	Class A, B, C Waters (CN)	0.02 mg/L	
MS	Freshwater: Acute	22 µg/L	
	Chronic	5.2 µg/L	
	Saltwater: Acute	1.0 µg/L	
	Chronic	1.0 µg/L	
MO	Amenable to Chlorination:		
	Chronic toxicity	5 µg/L	
	Acute toxicity	22 µg/L	
NV	Single Value	0.052 mg/L	
	24-hour average	0.0035 mg/L	
	Propagation of wildlife	0.005 mg/L	
NY	Surface Waters & Groundwaters (CN)		
	A, A-S, AA, AA-S, B, C	5.2 µg/L	
	D	22 µg/L	
	SA, SB, SC	1.0 µg/L	
	SD	1.0 µg/L	
ND	Class I Streams (total cyanides)	0.005 mg/L	
NC	Freshwater	5.0 µg/L	
PR	Coastal Estuarine Waters	20.0 µg/L	
	Surface Waters	20.0 ug/L	
OK	Acute	45.93 µg/L	
	Chronic	10.72 µg/L	

Table 7-1. Regulations and Guidelines Applicable to Cyanide (continued)

Agency	Description	Information	References
STATE (cont.)			
OH	Outside Mixing Zone (Max. free cyanide)		
	Cold water	46 µg/L	
	Limited resource warm water	22 µg/L	
	30-day average-cold water	5.2 µg/L	
	Inside Mixing Zone (Max)		
	Cold water	45 µg/L	
	Limited resource warm water	92 µg/L	
VA	Freshwater (total cyanide)	5.2 µg/L	
	Saltwater (total cyanide)	1.0 µg/L	
VT	Acute	22 µg/L	
	Chronic	5.2 µg/L	
WY	Special A Waters	0.005 mg/L	
WI	Great Lakes (free cyanide)	22.4 µg/L	
	Cold water	22.4 µg/L	
	Warm water sport fish	46.2 µg/L	
	All others	46.2 µg/L	
	Water Quality: Agricultural Uses		
AZ	Agricultural Irrigation (AgI)	No numerical standard	
	Livestock Watering (Ag I)	200 µg/L, T	
NV	Ag L	0.2 mg/L	
	Groundwater Monitoring		CELDS 1994
AL		Yes	
CA		Yes	
CO		Yes	
IL		Yes	
KY		Yes	
LA		Yes	
MN		Yes	
MT		Yes	
NY		Yes	
OH		Yes	
SC		Yes	
TN		Yes	
VA		Yes	
WI		Yes	
WV		Yes	

Table 7-1. Regulations and Guidelines Applicable to Cyanide (continued)

Agency	Description	Information	References
STATE (cont.)			
	Restricted Pesticides		
AL		Yes	
CA		Yes	
FL		Yes	
HI		Yes	
ME		Yes	
MI		Yes	
MT		Yes	
NH		Yes	
NY		Yes	
NM		Yes	
OR		Yes	
TX		Yes	
WA	.	Yes	
	Hazardous Constituents		CELDS 1994
AL		Yes	
CA	Land Disposal Restrictions	Yes	
CO		Yes	
DE	Land Disposal Restrictions	Yes	
IN	Allowable Concentration Using Leaching Test Method:		
	Class IV	0.2 mg/L	
	Class III	2 mg/L	
	Class II	5 mg/L	
IL		Yes	
KY		Yes	
LA	Reportable Quantity (HCN)	100 lbs	
MA	Land Disposal Restrictions	Yes	
MD		Yes	
ME		Yes	
MN		Yes	
MT		Yes	
NH		Yes	
NJ		Yes	
NE			

Table 7-1. Regulations and Guidelines Applicable to Cyanide (continued)

Agency	Description	Information	References
STATE (cont.)			
ND		Yes	
NY		Yes	
OH		Yes	
SC		Yes	
VA		Yes	
VT		Yes	
WI		Yes	
WV		Yes	
WY		Yes	

[a]Not classified as to its human carcinogenicity.

ACGIH = American Conference of Governmental Industrial Hygienists; avg = average; BAT = Best Available Technology Economically Achievable; BPT = Best Practicable Control Technology Currently Available; Ca = agent recommended by NIOSH to be treated as a potential occupational carcinogen; CELDs = Compute-aided Environmental Legislative Databases; CFR = Code of Federal Regulations; DWS = Domestic Water Source; EPA = Environmental Protection Agency; FBC = Full Body Contact; FC = Fish Consumption; FDA = Food and Drug Administration; FSTRAC = Federal State Toxicology and Regulatory Alliance Committee; HA = Health Advisories; IARC = International Agency for Research on Cancer; IRIS = Integrated Risk Information System; MCL = Maximum Contaminant Level; MCLG = Maximum Contaminant Level Goal; Mwh = megawatt hour; NAS = National Academy of Sciences; NATICH = National Air Toxics Information Clearinghouse; NCP = National Contingency Plan; NIOSH = National Institute for Occupational Safety and Health; NPDES = National Pollution Discharge Elimination System; NSPS = New Sewage Performance Standards; ODW = Office of Drinking Water; OERR = Office of Emergency and Remedial Response; OSHA = Occupational Safety and Health Administration; OSW = Office of Solid Waste; OTS = Office of Toxic Substances; OWRS = Office of Water Regulations and Standards; PBC = Partial Body Contact; PCBs = Polychlorinated Biphenyls; PEL = Permissible Exposure Limit; POTW = Publicly Owned Treatment Works; PSES = Pretreatment Standards for Existing Sources; PSNS = Pretreatment Standards for New Sources; RfC = Reference Concentration; RfD = Reference Dose; REL = Recommended Exposure Limit; SNARL = Suggested No-Adverse-Response Level; SOCMI = Synthetic Organic Chemical Manufacturing Industry; TLV = Threshold Limit Value; TSDF = Treatment, Storage, and Disposal Facility; TWA = Time-weighted Average; VOC = Volatile Organic Compounds; WHO = World Health Organization

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9. GLOSSARY

Acute Exposure-Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption Coefficient (K_{oc})-The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)-The amount of a chemical adsorbed by a sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Bioconcentration Factor (BCF)-The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Cancer Effect Level (CEL)-The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen-A chemical capable of inducing cancer.

Ceiling Value-A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure-Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Developmental Toxicity- The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Embryotoxicity and Fetotoxicity-Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurred. The terms, as used here, include malformations and variations, altered growth, and in utero death.

EPA Health Advisory-An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH)-The maximum environmental concentration of a contaminant from which one could escape within 30 min without any escape-impairing symptoms or irreversible health effects.

Intermediate Exposure-Exposure to a chemical for a duration of 15-364 days, as specified in the Toxicological Profiles.

9. GLOSSARY

Immunologic Toxicity-The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

In Vitro-Isolated from the living organism and artificially maintained, as in a test tube.

In Viva-Occurring within the living organism.

Lethal Concentration (LO)(LC$_{LO}$)-The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

Lethal Concentration(50) (LC$_{50}$)-A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose (Lo) (LD$_{LO}$)-The lowest dose of a chemical introduced by a route other than inhalation that is expected to have caused death in humans or animals.

Lethal Dose ($_{50}$) (LD$_{50}$) - The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time ($_{50}$) (LT$_{50}$)-A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)-The lowest dose of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Malformations -Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level-An estimate of daily human exposure to a dose of a chemical that is likely to be without an appreciable risk of adverse noncancerous effects over a specified duration of exposure.

Mutagen-A substance that causes mutations. A mutation is a change in the genetic material in a body cell. Mutations can lead to birth defects, miscarriages, or cancer.

Neurotoxicity-The occurrence of adverse effects on the nervous system following exposure to chemical.

No-Observed-Adverse-Effect Level (NOAEL)-The dose of chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K$_{ow}$)--The equilibrium ratio of the concentrations of a chemical in n-octanol and water, in dilute solution.

Permissible Exposure Limit (PEL)-An allowable exposure level in workplace air averaged over an 8-hour shift.

q$_1$* - The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q$_1$ * can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually μg/L for water, mg/kg/day for food, and μg/m^3 for air).

9. GLOSSARY

Reference Dose (RfD)-An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the NOAEL (from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ)-The quantity of a hazardous substance that is considered reportable under CERCLA. Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity-The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Short-Term Exposure Limit (STEL)-The maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily TLV-TWA may not be exceeded.

Target Organ Toxicity-This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen-A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)-A concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a TWA, as a STEL, or as a CL.

Time-Weighted Average (TWA)-An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose (TD$_{50}$)-A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Uncertainty Factor (UF)-A factor used in operationally deriving the RfD from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

APPENDIX A

ATSDR MINIMAL RISK LEVEL

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U. S .C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99-4991, requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLS) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substancespecific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1-14 days), intermediate (15-364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

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MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as a hundredfold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health EffectslMRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agencywide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road, Mailstop E-29, Atlanta, Georgia 30333.

MINIMAL RISK LEVEL WORKSHEET

Chemical name: Cyanide
CAS number: 143-33-9
Date: August 1997
Profile status: Final
Route: [ ] Inhalation [x] Oral
Duration: [ ] Acute [x] Intermediate [ ] Chronic
Key to figure: 32
Species: rat

MRL: <u>0.05</u> [x] mg/kg/day [ ] ppm [ ] mg/m^3

<u>Reference</u>: National Toxicology Program. 1993. NTP Technical Report on Toxicity Studies of Sodium Cyanide Administered in Drinking Water to F344/N Rats and B6C3Fl Mice. United States Department of Health and Human Services, Public Health Service, National Institutes of Health. NIH Publication 94-3386.

<u>Experimental Design</u>: Ten male and ten female rats were given 0, 0.2, 0.5, 1.4 (males), 1.7 (females), 4.5 (males), 4.9 (females), or 12.5 mg/kg/day cyanide in the drinking water for 13 weeks, as sodium cyanide. At the end of the study, the animals were evaluated for histopathology, clinical chemistry, hematology, urine chemistry, and reproductive toxicity. The heart, kidneys, liver, lung, testes, and thymus were weighed. Complete histopathologic examinations were performed on all animals in the 0 and 12.5 mglkglday dose groups. Blood from the base study rats was collected on days 86 (males) and 93 (females), and from the supplemental study rats on days 5, 25, 45, and 92 for hematology and clinical chemistry. Urinalysis samples were collected from the rats on days 5,25,45, and 92. Vaginal cytology and sperm motility evaluations were performed for 12 days prior to sacrifice. Numbers of leukocytes, nucleated epithelial cells, and large squamous epithelial cells were determined from vaginal swabs to ascertain estrous cycle stage. Sperm motility, density, and spermatogenesis were evaluated at necropsy.

<u>Effects noted in study and corresponding doses</u>: Sperm motility and vaginal cytology examinations were performed on rats. Decreased left epididymis weight, left cauda epididymis weight, left testis weight, spermatid heads, and spermatid counts were observed at 12.5 mg/kg/day. At 1.4 and 4.5 mg/kg/day, significantly decreased weight of the left cauda epididymis and spermatozoa motility were observed; however, these effects alone were not considered to be adverse. For females, more time was spent in proestrus and diestrus stages and less time in estrus and metestrus stages in the 4.9 and 12.5 mg/kg/day dose groups. However, this was not considered to be an adverse effect.

<u>Dose endpoint used for MRL derivation</u>: 4.5 mg/kg/day, based on NOAEL for no reproductive effects in male rats

[x] NOAEL [ ]LOAEL

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Uncertainty factors used in MRL derivation : 100

[ ] 1 [ ] 3 [ ] 10(for use of a LOAEL)
[ ] 1 [ ] 3 [x] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [x] 10 (for human variability)

MRL = 4.5 mg/kg/day/100 = 0.05 mg/kg/day

Was a conversion factor used from ppm in food or water to a mg/body weight dose? yes
If so, explain: The doses based on water consumption as reported by the author were 0, 0.3, 0.9, 1.0, 2.7, 3.2, 8.5, 9.2,23.5, and 23.6 mg NaCN/kg/day. These doses were converted from sodium cyanide to cyanide by multiplying each dose by 0.53 (CN-/NaCN); resulting in dose levels of 0, 0.2, 0.5, 1.4 (males), 1.7 (females), 4.5 (males), 4.9 (females),or 12.5 mg/kg/day cyanide.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: N/A

Was a conversion used from intermittent to continuous exposure? No
If so, explain:

Other additional studies or pertinent information that lend support to this MRL : This study showed reproductive effects at all dose levels. The effects noted at 1.4 and 4.5 mg/kg/day, significantly decreased weight of the left cauda epididymis and spermatozoa motility, were not considered by themselves to be adverse. However, at 12.5 mg/kg/day, a large number of reproductive effects were noted, which were considered to be adverse.

Other studies on cyanide support this MRL. Increased resorptions were noted in rats following oral exposure to cyanogenic glycosides in a cassava diet (Singh 1981), and increased gonadal weight in male rats exposed to copper cyanide (Gerhart 1986) or potassium silver cyanide (Gerhart 1987) for 90 days were noted. A reduction in the spermatogenic cycle and testicular germ cell sloughing and degeneration were noted in dogs fed rice with sodium cyanide added, while no reproductive effects were noted in dogs fed a cassava diet (Kamalu 1993). A LOAEL of 1.04 mg/kg/day based on systemic and reproductive effects in dogs was identified (Kamalu 1993). However, this study was not used to derive the intermediate oral MRL because dogs are not a good model for human toxicity. This is because dogs have very low levels of rhodenase, an enzyme which is used to detoxify cyanide.

Agency Contact (Chemical Manager): Carolyn Harper

APPENDIX B

USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (2-1, 2-2, and 2-3) and figures (2-l and 2-2) are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, minimal risk levels (MRLs) to humans for noncancer endpoints, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse- Effect Levels (NOAELs), Lowest-Observed- Adverse-Effect Levels (LOAELs), or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 2-l and Figure 2-l are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 2-1

(1)   Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exists, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 2-1,2-2, and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2-l) and oral (LSE Figure 2-2) routes. Not all substances will have data on each route of exposure and will not therefore have all five of the tables and figures.

(2)   Exposure Period Three exposure periods - acute (less than 15 days), intermediate (15-364 days), and chronic (365 days or more) are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to

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health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) <u>Health Effect</u> The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) <u>Key to Figure</u> Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the 2 "18r" data points in Figure 2-l).

(5) <u>Species</u> The test species, whether animal or human, are identified in this column. Section 2.4, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 2.3, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) <u>Exposure Frequency/Duration</u> The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 1 S), rats were exposed to toxaphene via inhalation for 6 hours per day, 5 days per week, for 3 weeks. For a more complete review of the dosing regimen refer to the appropriate sections of the text or the original reference paper, i.e., Nitschke et al. 1981.

(7) <u>System</u> This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermaYocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, 1 systemic effect (respiratory) was investigated.

(8) <u>NOAEL</u> A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.0005 ppm (see footnote "b").

(9) <u>LOAEL</u> A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less serious LOAEL of 10 ppm. MRL's are not derived from Serious LOAELs.

(10) <u>Reference</u> The complete reference citation is given in chapter 8 of the profile.

(11) <u>CEL</u> A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CEL's are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

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(12)   Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.0005 ppm.

LEGEND

See Figure 2-1

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13)   <u>Exposure Period</u> The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.

(14)   <u>Health Effect</u> These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15)   <u>Levels of Exposure</u> concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m3 or ppm and oral exposure is reported in mg/kg/day.

(16)   <u>NOAEL</u> In this example, 18r NOAEL is the critical endpoint for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates to a NOAEL for the test species-rat. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.0005 ppm (see footnote "b" in the LSE table).

(17)   <u>CEL</u> Key number 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18)   <u>Estimated Upper-Bound Human Cancer Risk Levels</u> This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (qt *).

(19)   <u>Key to LSE Figure</u> The Key explains the abbreviations and symbols used in the figure.

SAMPLE

TABLE 2-1. Levels of Significant Exposure to [Chemical x] – Inhalation

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect)		Reference
					Less serious (ppm)		
INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
Systemic	↓	↓	↓	↓	↓		↓
18	Rat	13 wk 5d/wk 6hr/d	Resp	3 [b]	10 (hyperplasia)		Nitschke et al. 1981

CHRONIC EXPOSURE

						11	
Cancer						↓	
38	Rat	18 mo 5d/wk 7hr/d				20	(CEL, multiple organs)	Wong et al. 1982
39	Rat	89–104 wk 5d/wk 6hr/d				10	(CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79–103 wk 5d/wk 6hr/d				10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

[a] The number corresponds to entries in Figure 2-1.

[b] uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

CEL = cancer effect level; d = days(s); hr = hour(s); LOAEL = lowest-observed-adverse-effect level; mo = month(s); NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)

1 →

2 →

3 →

4 →

12 →

SAMPLE

13 → **Figure 2-1. Levels of Significant Exposure to [Chemical X] – Inhalation**

Acute
(≤14 days)

Intermediate
(15-364 days)

Systemic

Systemic

14 →

15 → (ppm)

Death

Respiratory

Hematological

Death

Respiratory

Hematological

Hepatic

Reproductive

Cancer*

10000

1000

100

10

1

0.1

0.01

0.001

0.0001

0.00001

0.000001

0.0000001

16 →

16r 17r   24g 18r 18r   20m 22g 21r 20m   31r 30r   28m 22m 29r   35m 37m 34r 34r   27r   40m 38r 39r

33r

18r

17 →

18 → Estimated Upper Bound Human Cancer Risk Levels

10^{-4}

10^{-5}

10^{-6}

10^{-7}

Key

r Rat	● LOAEL for serious effects (animals)	∣ Minimal risk level for effects
m Mouse	◐ LOAEL for less serious effects (animals)	∣ other than cancer
h Rabbit	○ NOAEL (animals)	▼
g Guinea Pig	◆ CEL - Cancer Effect Level	The number next to each point
k Monkey		corresponds to entries in the accompanying table.

* Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer end point.

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APPENDIX B

Chapter 2 (Section 2.5)

Relevance to Public Health

The Relevance to Public Health section provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health endpoints by addressing the following questions.

> 1. What effects are known to occur in humans?
>
> 2 . What effects observed in animals are likely to be of concern to humans?
>
> 3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The section covers endpoints in the same order they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). In vitro data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this section. If data are located in the scientific literature, a table of genotoxicity information is included. The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal risk levels (MRLs) for noncancer endpoints (if derived) and the endpoints from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, we have derived minimal risk levels (MRLs) for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action; but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2.5, "Relevance to Public Health," contains basic information known about the substance. Other sections such as 2.7, "Interactions with Other Substances," and 2.8, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses for lifetime exposure (RfDs).

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To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

APPENDIX C

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADME	Absorption, Distribution, Metabolism, and Excretion
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
BSC	Board of Scientific Counselors
C	Centigrade
CDC	Centers for Disease Control
CEL	Cancer Effect Level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
CLP	Contract Laboratory Program
cm	centimeter
CNS	central nervous system
d	day
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DOL	Department of Labor
ECG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
EKG	see ECG
F	Fahrenheit
F_1	first filial generation
FAO	Food and Agricultural Organization of the United Nations
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
fpm	feet per minute
ft	foot
FR	*Federal Register*
g	gram
GC	gas chromatography
gen	generation
HPLC	high-performance liquid chromatography
hr	hour
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
IL0	International Labor Organization
in	inch
kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{LO}	lethal concentration, low

APPENDIX C

LC$_{50}$	lethal concentration, 50% kill
LD$_{LO}$	lethal dose, low
LD$_{50}$	lethal dose, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
mg	milligram
min	minute
ml	milliliter
mm	millimeter
mmHG	millimeters of mercury
mmol	millimole
mo	month
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
ng	nanogram
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPL	National Priorities List
NRC	National Research Council
NTIS	National Technical Information Service
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
PEL	permissible exposure limit
Pg	picogram
pm01	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
PPb	parts per billion
mm	parts per million
PPt	parts per trillion
REL	recommended exposure limit
RfD	Reference Dose
RTECS	Registry of Toxic Effects of Chemical Substances
set	second
SCE	sister chromatid exchange
SIC	Standard Industrial Classification
SMR	standard mortality ratio
STEL	short term exposure limit
STORET	STORAGE and RETRIEVAL
TLV	threshold limit value
TSCA	Toxic Substances Control Act

APPENDIX C

TRI	Toxics Release Inventory
TWA	time-weighted average
U.S.	United States
UF	uncertainty factor
yr	year
WHO	World Health Organization
wk	week

>	greater than
$\geq$	greater than or equal to
=	equal to
<	less than
$\leq$	less than or equal to
%	percent
α	alpha
β	beta
δ	delta
γ	gamma
μm	micrometer
μg	microgram